

RATIONAL ORGANOTHERAPY

WITH REFERENCE TO UROSEMIOLOGY

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RATIONAL ORGANOTHERAPY

INTRODUCTION

IN Medicine in all ages many general problems have been proposed, and such a problem was contained in the idea of replacing the destroyed or disturbed function of an organ by a similar one from another individual. Hypothetical reflections of this kind formed the dreams of physicians of the earliest ages. The Kawa-Soutra mentioned in Sanskrit (a decoction of bucks' testicles in milk) had already been used by the ancient Hindus as strength-giving means. Although superstition and mysticism were at the bottom of these early endeavours, the history of Medicine shows on the other hand that from Hippocrates' day an empiric organotherapy had become established in Medicine, and that some systematic investigations were made in this direction; for already it was deemed practicable to replace remedies whose natures were foreign and often harmful to the system by others which were not only innocuous but were of a nature akin to the organisms to which they were applied.

§ 1. An empiric organotherapy was practised in ancient times

And here it must be said that in the past, as well as to-day, Organotherapy had its enemies, as F. Brunet (*Arch. clin. de Bordeaux*, 1898, Nos. 2-4) reports in his history of Organotherapy. But we must restrict ourselves to mentioning that opponents of Organotherapy have been for long upbraided with not comprehending the most important biological problems which Organotherapy sets forth, inasmuch as it claims to unveil long-hid secrets of many physiological and pathological phenomena.

The interesting investigations of the famous French physiologist, Brown-Séquard, who inaugurated a new era in Medicine, must be looked upon as the turning-point in the history of Organotherapy. As a result of his investigations

§ 2. Brown-Séquard's doctrine of the inner secretion

the new doctrine of the so-called "Inner Secretion" appeared, according to which some glands produce substances which pass over from them directly into the blood and the juices of the organism, and in this way exercise an influence on the general metabolism of the body.

This new doctrine, which is full of the deepest scientific interest, soon attracted the attention of scientists, many of whom entered upon an experimental study of the question. The result of these investigations was that the new doctrine received scientific sanction, and new and wider horizons were opened to Medicine.

In this doctrine of the inner secretion of the glands Organotherapy originated; not empiric, as formerly, but rational, being based on well-defined scientific facts.

§ 3. The
necessity of
absolute
harmlessness
of organo-
preparations

And here it must be observed that Organotherapy was comparatively free from danger as long as the organo-compounds were only administered internally. From the moment, however, that Brown-Séquard introduced the hypodermic injections of organo-extracts the danger became great. The filtration of the extracts through kaolin-sticks, which was suggested by the French school (Chamberland and d'Arsonvale), proved insufficient; as only the microbes themselves—but not their products—and other toxins dissolved in the extracts, are excluded. We should therefore recognise as highly reasonable the endeavours of the chemists of to-day to isolate the active principles from the organs, or, if for any reason this be not feasible, the method of preparing organo-compounds suggested by Prof. von Poehl². By this method all toxic products are eliminated. In this form the treatment with animal organs is absolutely free from danger, because nothing which is foreign to it is introduced into the diseased organism, but only that which is necessary for its normal functions. So physiological and therefore perfectly harmless a method of treatment deserves our special attention, as well for the reason that in its application we run no risk of violating the fundamental law which a physician should never forget—"primum ne noceas."

To a method so strictly scientific there can be no opposition: a position hostile to Organotherapy would be identical with negation of the physiology and pathology on which it is based.

From time to time some over zealous critics appear who hold a sceptical position against Organotherapy and explain its results as the outcome of suggestion. Such scepticism, however, is generally caused by ignorance of the literature of the subject. If all these critics would first familiarise themselves with its literature they would easily realise how false it is to attribute all the results of Organotherapy to the influence of suggestion. As a matter of fact, what suggestion could be taken into consideration in the case of experiments and observations on animals, on insane persons with dull sensory, or on children of tender age, or on unconscious people, from whatever cause the unconsciousness arises?

Neither is Organotherapy in opposition to the principles of cellular pathology, if, as it ought to be, by it is meant the totality of all those morphological and chemical phenomena by which the normal course of the cellular life is directed. However, cellular life can also be impaired from the absence of all visible morphological changes when the chemical processes in the cellular metabolism are impaired. Indeed, there is a whole series of so-called functional affections which are characterised by no perceptible anatomical changes whatever. As examples of this neurasthenia, hysteria, hemicrania, certain forms of epilepsy, various poisonings, etc., may serve. It is not visually possible in such cases to find any morphological changes in the organism. However, in these as well as in many other diseases we can easily understand their nature when looking at the results of the chemical analysis of the excretions of the organism. The urinalysis, with special consideration of the co-efficients of the urine, furnishes in these cases the key to the proper solution of the problem. From such a chemical point of view the nature of a whole series of diseases which before were perfectly mysterious is easily understood. Now we know that they are caused by some disturbance of the metabolism in the organism. We know also that the metabolism in a high degree depends on the products of the inner secretion of different glands. In this way Organotherapy is of great importance in the treatment of different anomalies of the metabolism of cells or tissues following on disturbances of the function of any organ. In fact, by the use of certain organo-therapeutic preparations in proper cases a desired result can be

§ 4. The explanation of organo-therapeutic results by suggestion is beyond criticism

§ 5. Organotherapy influences the chemistry of the metabolism

obtained which will show itself not only in an improvement of the general health, but also in the disappearance of many pathological symptoms.

A perfectly objective and therefore still more convincing proof of the improvement in the condition of the patient is furnished by the urinalysis, from which the degree of the therapeutic effect may be estimated.

§ 6. Serothe-
rapy is also
organothe-
rapy (patho-
logical)

Serotherapy must be considered along with Organotherapy, but to a certain degree only. Organotherapy uses the normal products of healthy animals, while serotherapy borrows its means from men and animals who have gone through a natural or an artificially produced disease. If the so-called antitoxins, the active principles of serotherapy, could be gained from healthy animals, serotherapy would coincide with Organotherapy. As long as this is not the case we have the right to consider serotherapy as a "pathological organotherapy" which does not belong to our department. We shall therefore content ourselves by referring to their connection only as touching the question of immunity. In this book we set ourselves not only the task of demonstrating in what cases we may expect results from Organotherapy and in what cases compounds of Organotherapy have already been useful, but also to show in what manner the beneficial influence of organo-preparations can be accounted for on the basis of physiological-chemical observations.

§ 7. Division
of labour
between the
authors

In order the better to accomplish our purpose the work of writing this book was divided: Prof. Prince J. v. Tarchanoff, who personally undertook the necessary experiments on animals, accepted the physiological part; Prof. A. v. Poehl, who deals with the chemical questions of Organotherapy in connection with the urinalysis, took upon himself the physiological-chemical part; and Dr. Wachs, who as collaborator in the "Russian Journal for Medical Chemistry and Organotherapy" is acquainted with the literature of our subject and the therapy of the organo-preparations, has composed the clinical part of the work.

It is perhaps necessary to say that it is not our intention to go into details, but simply to view the question from such standpoints as are necessary to accomplish our purpose.

Those who take an interest in Organotherapy and who desire to become better acquainted with it may note that the

editors of the "Russian Journal for Medical Chemistry and Organotherapy" are willing to supply any who wish it with all possible information about the question of the therapeutic use of the different organo-preparations. Experimentalists on their part are requested to communicate to the editors of the journal their observations in this direction.

CHAPTER I

WHAT ARE THE OBJECTS OF A RATIONAL ORGANOTHERAPY?

§ 8. Can we expect to gain from dead animal tissues any therapeutically active elements?

FOR a scientific, rational Organotherapy, it is before everything else of the utmost importance to discuss the question of the lability and destructibility of the living matter which forms the bulk of living tissues and organs of the animal organism. If we assume, as often has been done, that the living matter possesses so great a lability and is so easily decomposed that in the moment of death, as well as under the influence of chemical agencies, it falls apart into more simple compounds, the possibility of gaining from dead animal tissues and organs any substances which they contain only *intra vitam*, is, of course, excluded.

§ 9. The unfitness of the customary organo-therapy and the necessity of the active constituents.

Guided partly by this idea of the great lability and destructibility of living matter, Brown-Séquard, the founder of modern Organotherapy, held that for the purpose of extracting the active principles from any animal organ it should be removed in the freshest possible condition immediately after the animal has been killed, and that only some watery or glycerin extracts must be made, because the complicated structure of the matter concerned is then the least injured. In this way his often mentioned emulsion of testicles was prepared. It contained, however, not only the active constituents, but also all the other products, including even the various pathogenic elements which, if the animal were affected with any germ-disease, might be present. Brown-Séquard gave his emulsion the preference partly also because his imperfect knowledge of the active constituents led him to believe that they could not be isolated.

If there were really so great an instability in the living matter, the death and the comminution, as well as the treatment with water, would be sufficient to cause destruction. In the first place, however, a mixture of the very different

products of assimilation and disassimilation extracted from the organs is certainly not fit to be injected hypodermically into a sick person as a therapeutic, seeing we have to deal with unknown elements. Such a procedure is not in keeping with scientific methods. Science demands before everything else a clear definition of the factors participating in the phenomenon. The objection that the substances gained in pure form from the organs could by no means be the principle active during life is refuted by the comparative examination of the effects of the isolated constituents on the organism on one side and the effects of the organ-extracts on the other. If the effects of the physiological action in both cases agree, the isolated substance is also the looked-for specific agent. The dosage generally plays an important part in therapeutics. This, however, can only take place with known substances. A dosage of uncertain and unknown organ-extracts is out of the question. Already this alone ought to place the use of organ-extracts in the background, and that of the isolated substances in the foreground. Finally the unfitness of the organ-extracts, as already stated, is clear from the fact that with them different parasites with which the animals are infected, and which were not diagnosed before the organs were used, might be transferred to the patient. The parasites can be removed by filtration of the extract through kaolin sticks. The toxins, however, as Prof. Poehl³ has demonstrated, are not removed. Of the supposed advantages of the extracts apparently not one remains, and now all that is needed is proof that the endeavours to gain the active specific elements of the organs or the juices of the body, in a pure condition, are no longer utopian. As an example of this Spermin—which was obtained in crystallised form from testicle extract by Prof. A. v. Poehl—may be cited. It shows the whole therapeutic action of Brown-Séquard's testicle-emulsion without possessing its negative qualities. The *adrenaline* of Takamine, as well as the *adrenalchloride* of Prof. Poehl, which has also been gained in crystallised form, possesses the therapeutic properties of the suprarenal glands. The *haemoglobin* which can be gained from the blood in crystallised form is, in an isolated condition, used as an organotherapeutic preparation. The *cholein salts* extracted from the gall also represent an organotherapeutic preparation. The *lactic acid*

§ 10. Possible presence of toxins in improperly made organ-extracts

§ 11. Isolation of the active constituents not utopian

which is produced in the animal tissues can also be looked upon as one of the isolated remedies of Organotherapy. It is used either as a hypnotic or applied with the brush in bacterial processes. Finally, a whole group of ferments belongs here—viz., *pepsin*, *trypsin*, and others.

The foregoing would be sufficient to show that the endeavours of the Organotherapy of to-day to gain the therapeutically active constituents of the organs in an isolated condition are no longer utopian. If the number of these isolated active constituents is still a very limited one, it is so only for the reason that in this direction one meets with some very great chemical obstacles which will, in all probability, be overcome in the future. In the meanwhile, we are forced to restrict ourselves to the use of preparations from the organs or of such of the active constituents as may not be perfectly pure.

§ 12. Syner-
getic groups

This rational endeavour of the Organotherapy of the present time to obtain the active constituents of the organs and the juices of the body in the cleanest and an entirely isolated condition is in no way opposed to the fact that in the treatment of disease the favourable results are not obtained through the influence of one certain constituent of an organ exclusively, but through the totality of the elements existing in that organ. With *choleinic acid* alone, for instance, or its salts, no such good results are obtained as with the rationally made preparation of the whole gall, which has been introduced for specific diseases. It contains also other active principles, and this perhaps for the reason that *choleinic acid* exerts its therapeutic influence only in the presence of other constituents of gall. A similar reasoning might, as we shall see further on, be applied to the *Cerebrinum-Pochl*, which does not represent a certain chemical constituent, but consists of a synergetic group of leucomaines of the grey matter of the brain. From clinical observations one might conclude that this natural mixture of leucomaines, which is obtained from the grey cortex of the brain, operates in a more energetic and reliable manner than the single constituents, that is, the single cerebroside of the brain. An analogous example might be quoted from the family of the vegetable alkaloids—namely, the fact that quinia isolated in a pure condition has in its therapeutic use by no means all the qualities of the whole quinia bark, etc. What has been said

gives sanction to the therapeutic employment (in certain cases) of preparations from organs which represent the totality of the active elements (synergetic group) which they contain, provided all the harmful and toxic constituents have been eliminated from them. However, in this case also, Organotherapy must remain faithful to its direct aim. It must endeavour to isolate the single active constituents of these organ-extracts, and to study their biological chemical qualities. After having changed, to precisely known quantities, these x , y , and z , which represent the constituents of different organo-therapeutic preparations, the Organotherapy of the future will be enabled to fight successfully against different diseases, with quantitative and qualitative graduations, through the influence of either the single active organ-elements or of unions of two or more of them. This is the ideal which a rational Organotherapy must never lose sight of. In the meantime it has in many cases, besides the use of single isolated organ-elements, to admit the therapeutic employment of preparations containing some synergetic groups, provided, however, that they be perfectly harmless and exercising a constant therapeutic influence in disease.

We therefore fully agree with P. F. Richter,⁴ that in Organotherapy preference shall always be given to therapeutically active constituents and, if this be impossible, we should be provisionally contented with rationally made preparations.

The foundations of a rational, scientific Organotherapy are, therefore, already established. The question still remains open, if and to what extent the idea of the great inconstancy and destructibility of living matter, which until recently has been upheld by some authors, is justified.

Before everything else, let us turn our minds to the remarkable vitality of many tissues and organs after the death of the organism. The heart has stopped, the respiration has ceased, the consciousness, every sensation and motion, have disappeared. We say life is extinct; still, the muscles of the warm-blooded animals and men retain their irritability and contractibility for an hour or more, and on direct irritation, as, *e.g.*, of the electric current, react by contraction. After the muscular irritability is gone, for a further two or three days after death a lively activity can be observed in the ciliac of the

§ 13. Vitality
of many
tissues or
organs after
death

ciliary epithelium; they move energetically. Finally, after this motion also has ceased, many leucocytes still remain alive. They execute amœboid movements and as wandering cells ramble about in the tissues of the corpse. Apparently, after what is customarily called death, the organs of the body do not lose their vital energies all at once, but by degrees. First the functions of the more complicated organs—viz., brain, muscles, glands—then those of the other organs expire successively, according to the lessening complexity of their structure. Hence the life of the organism goes through a complete series of interjacent stages covering a period of several days. This survival of the organs after death unmistakably proclaims the stability of the living matter. Further, the experiment shows that the cessation of the functions of the organs does not mean that they are really dead. Experiments for the revival even of amputated organs prove this clearly. Of this we have incontrovertible proofs in observations which comprise nearly all those organs which perform the most important physiological functions.

§ 14. Post-mortem vital activity of the muscles.

The muscles of the warm-blooded animals lose their irritability soon after their removal from the body. This, however, does not mean that they are already dead. All that is necessary is to restore in them an artificial circulation of the blood—e.g., with defibrinated blood warmed to the temperature of the body—and the functions of life will soon return and contractions will be produced by direct irritation. Such a restoration of life may last for hours, and the experiment may be several times repeated. If we proceed further we find the following: The *rigor mortis*, which even at the present time is taken for the most reliable sign of death, is, according to the experiments of Ernst Mangold⁵, unreliable, as the muscles even after having grown stiff may, under certain conditions, react again on strong electric irritation. The heart-muscle of the frog which has been stiffened by heat or by poison, according to the observations of Geibel⁶, may, after blood has been passed through the heart for some time, again contract. These facts have a high theoretical significance in the consideration of the question in which we are interested, and they indicate that, even after their stiffening, no absolute destruction occurs in the muscles. From this only one conclusion can be drawn, viz., that the living matter which in

such cases has hitherto been considered as absolutely dead is really not so, but preserves a functional activity for a long time.

We will next turn our attention to the secretory and excretory glands, and will first consider the liver and the kidneys. Of course, the functions of the liver as well as those of the kidneys cease soon after the death of the organism. All we have to do after their removal from the body, however, is to establish an artificial circulation of the blood in them with warmed defibrinated blood, and the liver will again secrete gall (Schmulevitsch⁷) and produce urea (Cyon⁸), while the kidneys will secrete urine. This may go on for hours. Besides, the kidneys continue their synthetical activity by producing hippuric acid out of glycocoll and benzoic acid (Schmiedeburg⁹). These observations are of special importance with regard to the fact that the synthetic action of an organ requires all the vital qualities of the protoplasma of the cell. We have therefore to concede to the living matter also a high degree of vitality, which survives the apparent death of the organism.

Even the brain, the most tender and complicated organ in the body, is no exception in this respect, although as is known, as the first sign of death consciousness ceases, and the sensibility and the function of the voluntary motions, *i.e.*, the direct functions of the cerebrum, disappear. The human head, after having been severed from the trunk by the guillotine, loses all its functions at once and seems to be perfectly dead. Only the facial muscles react for some time on direct irritation with the electric current. The nervous substance itself, especially the cortex of the hemispheres of the cerebrum, seems to be absolutely unirritable, and its chemical reaction is acid instead of weakly alkaline.

§ 15. Post-mortem irritability of the brain.

However, as Laborde¹⁰ and others did, one only needs to restore through the cerebral arteries an artificial circulation of the blood, with warm defibrinated blood, and the cortex of the brain regains its weakly alkaline reaction, while its irritability is restored, as is evident from the fact that an electric irritation of the psycho-motor centres produces corresponding motions in the facial muscles. Apparently also the brain is no exception, and the disappearance of its functions do not prove an entire destruction, an absolute death. Noteworthy in this respect is the survival of the central nervous system in cold-

blooded animals, as, for instance, in frogs. Prof. Setchenoff¹¹ has demonstrated that after the removal of the whole cerebro-spinal system some specially notable impulses and discharges occurred which took the form of negative fluctuations of the current and even of motions of the hind legs, which remained connected with the brain. In this way the living contents of even the most tender elements of the body have a well-pronounced duration of life, a vitality which is incompatible with the theory of a great lability and destructibility of the living matter.

§ 16. Revival
of the
isolated
heart.

A very remarkable example is furnished by the experiments recently made by Dr. Locke¹² and Prof. Kuliabko,¹³ as to the revival of the isolated heart of mammalia and men. They demonstrate the great vitality and the striking survival of the heart. By the use of the known solution of common salt with an admixture of grape-sugar, as recommended by Dr. Locke, the contractions of a cut-out heart of a warm-blooded animal can be kept up for hours and even days, and this activity, when recorded with the registering apparatus, appears hardly different from that of the normal heart. Prof. Kuliabko made great progress in this matter by demonstrating the possibility of the enlivening of the heart of warm-blooded animals, as well as of men, after death from different diseases, and this not only directly after death, but twenty-four or more hours later. Especially interesting was the enlivening of the heart of a child dead from double-sided pneumonia twenty hours after death. Even on the fifth day it reacted with contractions on being washed through with Locke's fluid: so great is the intensity of the vitality of the living contractile substance of the heart-muscle, or, in other words, the power of resistance of the living matter against destruction and decomposition.

§ 17. The
cessation of
the function
of the organs
in death is
not a conse-
quence of
destruction
of substance,
but chiefly
one of auto-
intoxication

It follows therefore that, if the heart of a man dead from any disease which does not affect the muscular and nervous apparatus of the heart stands still and does not work, this does not happen because the living substance of the heart-muscle is decayed, but because an accumulation of products of retrogressive metamorphosis in the heart which are not washed out and removed by the blood paralyses the activity of the neuro-muscular apparatus of the heart. One has only to pass Locke's salt-solution, which answers this

purpose very well, through the coronary arteries to make the heart beat again. Such an experiment may be repeated daily for several days on the same heart.

Hence it appears that the cessation of the functions of the organs and tissues at the time of the death of the organism in by far the great majority of instances is not caused by a quick, sudden destruction of the living matter constituting them, but by a poisoning of the tissues with products of decay which accumulate in the organs and tissues as the functions of life cease.

This fact, which became especially evident in the revivification of the heart of the warm-blooded animals, is of fundamental importance for Organotherapy. If the amount of the energy of the vital functions is really so intimately connected with the accumulation in the body of products of retrogressive metamorphosis, their destruction through intraorganic oxidation, their prevention from doing harm through chemical neutralisation, or finally their removal through an increased excretion, plays some very prominent parts in the health of the organism. As we shall see, *Sperminum-Poehl* may serve as representative of the first agent, while *Thyrodinum-Poehl* and *Glykocoll* may serve for the second, and *Cerebrinum-Poehl* for the third.

In general by the investigations on the resuscitation of the heart of the warm-blooded animals and men the importance of the chemistry of the body for the maintenance of the normal course of the vital functions, and consequently also the significance of Organotherapy, the main object of which is the regulation of the course of the chemical processes in the body, are appreciated properly.

From the foregoing sketch of the dying, the surviving and the revivifying of the organs, the vitality of the living matter constituting the tissues and organs appears with sufficient clearness as to point to a conclusion in direct opposition to the hitherto prevailing theory of the great lability and destructibility of living matter.

The verification of this assertion, as mentioned before, has an enormous significance for Organotherapy, as only if it be correct, can one expect to isolate, by the use of different chemical procedures from fresh organs and tissues, the *intra vitam* active chemical elements.

§ 18. For the resuscitation of the organs the products which cause the retrogressive autointoxication must be removed—a principle of organotherapy

An extensive list of the *intra vitam* active compounds obtained from the tissues and organs fully confirms these expectations.

§ 19. Indications and production of ferments and katalysators from the organism

In the first place let us consider the large group of ferments and katalysators which play so great a part in the metabolism of the body. It is, of course, generally known that the chemistry of the living organism, which is the foundation of the metabolism, is a process *sui generis* which differs in some regards from the processes of the anorganic life. As foundation of the chemistry of the living organism is the following principle, namely—the attainment of the necessary results at the least expense of power and time. To this phrase answers in the full meaning of the term the very important group of chemical compounds produced by the living cells which form the group of the ferments and the group of katalysators appertaining to them.

§ 20. The activity of the ferment is independent of the life of the cell

Let us first speak of the former. Until recently it was customary in science to separate the ferments into two subdivisions, viz., the organised and the non-organised ferments. As a necessary condition for the activity of the former the life appears, that is, the living condition of the cell-organisms themselves that produce any kind of fermentation, as, for instance, alcoholic, lactic acid, butyric acid, acetic acid, marsh-gas, and putrid fermentation. The discriminating sign of the non-organised ferments is that they can be extracted from the gland-cells by which they are produced with preservation of their physiological qualities. The cell-life as such is here not necessary. To this category belong all the so-called digestive ferments. Such a difference, however, cannot be considered as qualitative since Marie Manasseïn,¹⁴ by investigations made in the laboratory of Wiesner, first demonstrated that the most typical representative of the organised ferments, the beer-yeast-cells, in a perfectly mortified condition are able to produce alcoholic fermentation, though in a comparatively very weak degree only. They succeeded even in gaining from absolutely dead yeast-cells a watery extract which possessed the faculty of producing alcoholic fermentation. These investigations attracted the special attention of the famous chemist Liebig. Later the Munich hygienist Buchner made an important step ahead by improving the methods and isolating from the

beer-yeast-cells the active principle of the alcoholic fermentation, but in extremely small quantities. This important fact entitles us to assume that other so-called organised ferments will follow the same rule, and that consequently in the principle there are no reasons why a sharp distinction between organised and non-organised ferments should be made. One as well as the other is formed in the protoplasm of the living cells and may cause some chemical processes, according to circumstances, inside or outside of the cells.

This excludes the assumption of a sharp distinction between the so-called organised and non-organised ferments.* It remains, however, to mention a series of ferments which were extracted from the tissues and organs of the "animal body" and which doubtless play an important part in the economy of the animal organism. From the salivary glands and the pancreas an amylolytic ferment, which changes starch to sugar, has been obtained. From the pepsin-glands of the stomach *pepsin* and from the pancreas *trypsin* have been produced, two ferments which peptonise albumen. The former is active in acid reaction only, the latter exclusively in alkaline. Further, from the mucous membrane of the stomach the so-called *labferment* was gained, which makes the kasein of the milk coagulate. From the pancreas a ferment has been obtained which splits fats into glycerin and fatty acid and promotes the saponification of fats. Finally in the juices of the intestines a "ferment of the ferments" (*enterokinosis*) has recently been discovered (Prof. Pavoloff¹⁵) which plays the part of a positive katalysator and accelerates the activity of all the above-mentioned amylolytic, proteolytic, and fat-splitting ferments. All these bodies belong to the digestive ferments; they all operate in the course of life, being secreted into the digestive canal together with the juices from the respective organs. Through certain proceedings of physiological chemistry they can be extracted from the organs as well as from the digestive juices secreted by them. The qualities of these active mediators of digestion tally exactly with the ferments, that is, they influence the reactions without suffering destruction. In small quantities they produce changes in a

* As we shall see further on, there is also no sharp distinction between ferments and katalysators.

large quantity of substances. They can be destroyed with comparative ease, they cannot stand high temperature (over $60^{\circ}\text{C}.$), and they suspend their activity as soon as a certain quantity of the products of their change has accumulated. In spite of the tenderness of these bodies, which shows itself principally in an evident sensitiveness for comparatively high temperature ($60^{\circ}\text{C}.$), they can be extracted, as we shall see, from organs and digestive juices through fairly complicated chemical proceedings. They have found extensive employment in Medicine for a considerable period. These isolated digestive ferments furnish a good example of rational Organotherapy.

Such a digestive Organotherapy alone ought to have long since called the attention of the authors to similar therapeutic agents in the tissues and organs. This, however, did not occur because other organs and tissues (besides the digestive glands) showed no secretions that were demonstrable until then. From the moment, however, that Brown-Séquard¹⁶ procured scientific recognition for the theory of an "inner secretion," work in this direction commenced, and to-day quite a series of organotherapeutic preparations of the highest value are placed before us.

§ 21. Isolated chemical substances, like spermin and adrenalin, are physiological katalysators

To the ferments belongs an important group of compounds, the *katalysators*, that is such bodies as by their presence alone and in infinitesimal quantities are enabled to accelerate or to retard a reaction without suffering on their part any loss of weight. In the first case we have to deal with positive katalysators, and in the second with negative ones. The positive katalysators, according to Ostwald¹⁷, play, so to say, the part of the oil applied to the axis of the wheel for the purpose of decreasing the friction. The movements of the wheels are accelerated, but the propelling force is not in the least increased. Further, the oil, like the katalysators, is not destroyed by the function. This is one of the most simple forms of explaining the activity of the katalysators. It was devised by Ostwald in the year 1894. Furthermore it is of great importance that in those cases in which two or more katalysators exercise a mutual activity, there is often a much greater increase produced than could be expected from the addition of the single factors. Finally, cases are possible in which a katalysator, which did not exist at the beginning of

the reaction, originates through the course of the reaction, and in this way, so to speak, an "autokatalysis" is produced. As an argument in favour of the latter Ostwald quotes the solution of metals in nitric acid. The nitrous acid which is formed thereby accelerates the action of the nitric acid and in this way the "lazy" acid (which the nitric acid is in relation to copper) becomes decidedly more active. As proof of the assertion that two katalysators in combined action cause a much larger acceleration than is shown by the addition of their individual actions, the fact may be quoted that by the simultaneous action of cuprions and ferrions an increased quantity of ions capable of reacting is formed. Anyhow the katalytic processes are naturally beyond comparison more complicated than the effects of the oil poured on the axle of the wheel, but their further investigation belongs to the future.

Ostwald attributes to the katalysators a very important task in the economy of the organism, especially in the processes of oxidation which chiefly constitute the foundation of the development of the living forces. Such an opinion, as we shall see later (Poehl¹⁸), is corroborated by the physiological action of *Spermin* in the organism. Takamine¹⁹, contemporaneously with Aldrich²⁰, and later on also Prof. Poehl,²¹ separated from the suprarenal glands a crystalline substance — *adrenalin-Takamine* or *adrenalchloride-Poehl*,* the physiological action of which is opposed to that of *Spermin*, which means that *adrenal* accelerates the processes of reduction and *Spermin* those of oxidation. This is proved by chemical and physiological experiments with which we shall deal later. These two compounds, namely, *Spermin* and *Adrenal*, are so far the only two katalysators which have been isolated from the organs in pure crystallised form.

To the series of the katalysators which accelerate the excretion of the textural respiration belongs *cerebrinmm-Poehl*, which according to the experiments of Poehl²² accelerates the removal of the products of decomposition, especially of the nervous tissue. This preparation is not yet a well-defined, isolated chemical substance, but a synergetic group.

§ 22. Katalysators contained in synergetic groups of organo-preparations

* As the name "adrenalin" from the point of view of the customary terminology is incorrect and might lead to misunderstanding, Prof. Poehl has proposed the name "adrenal." The muriate of adrenal is adrenalchloride or chloradrenal.

Other preparations which were gained from tissues and are extensively employed in Organotherapy, such as *thyroidin*, *epiphysin*, *mammin*, *ovarin*, *suprarenalin*, also represent, in a chemical sense, some substances obtained from the respective organs. As to the question to which group of compounds they belong as judged from their katalytic action, very little can at present be said that would be beyond discussion, from lack of observation of their influence on the metabolism. When dealing with the physiological action of organo-therapeutic preparations we shall return to these compounds. So far we can only say that there are good reasons why we should assume that the majority of the individual bodies which form the synergetic groups of these organo-therapeutic preparations will sooner or later enter into therapy as isolated bodies. Such a hope is justified by the results obtained in the laboratory and from the clinical observations that have been made with *Spermin*, *Adrenal*, etc.

§ 23. The life causes the formation of products of retrogressive metamorphosis the removal of which brings about the textural respiration

The normal course of the metabolism is one of the chief considerations in the normal life of the organism. In the life of the cells we find mainly two groups of chemical processes. One group is formed by the synthetical processes which from compounds of small molecular weight produce others of greater weight. These synthetical processes take place in the cells chiefly in the neighbourhood of the nucleus (A. Gautier²³). Mainly they constitute various processes of reduction, and occur with weak acid reaction. Their work is to provide the material necessary for life.

The other group of vital processes of the cell belongs to the so-called analytical ones. There are also some processes which are of the greatest interest to us from a medical point of view. They are the processes of the removal of the products of decomposition which are necessarily formed by the vital activity of the cell. These processes are characteristic in that from compounds of great molecular weight owing to falling apart, splitting, oxydation, hydration, etc., some compounds of smaller molecular weight are formed, whereby from compounds not readily soluble some easily soluble ones are formed, which are more easily removed from the organism. As appears from the investigations of A. Gautier, these analytical processes, which belong to the textural respiration, take place chiefly in the outer part of the cell. They are

characterised first by processes of oxidation and occur in alkaline reaction.

As cellular and textural activity cannot exist without the disintegration of albuminous substances the removal of the products of decomposition of albumen is one of the most important vital functions, because their accumulation necessarily has a deleterious influence on the normal functions of the cell and the tissue.

Such disturbances of the functions of the textural and cellular life as depend on an accumulation of products of decomposition or metabolism form a very frequent cause of disease which Bouchard²⁴ aptly named disease from self-poisoning (auto-intoxication).

Until recently many medical authorities recognised symptoms of auto-intoxication only when products of poisonous (toxic) nature are formed and retained in the organism. Such products are in fact very often formed there; *e.g.*, different xanthin-compounds (xanthin, hypoxanthin), cholin, neurin, etc. Besides these normal toxic products of metabolism other poisonous products of decomposition of albumen are formed, partly during pathological disturbances of the metabolism, partly under the influence of the vital activity of pathogenic micro-organisms. Although diseases from the accumulation of poisonous products of decomposition of albumen doubtless occur and are observed, they form a very small fraction only of the cases with which every physician has to deal. He has very often to deal with auto-intoxication from the accumulation of quite indifferent substances, as, *e.g.*, uric acid (Haig, Poehl²⁵), etc. The latter compound, although it is generally not considered poisonous, interferes with the normal functions of the nervous and muscular tissues by its accumulation in the cell or tissue, and produces a whole group of the most variable pathological symptoms (Haig²⁶).

That auto-intoxication is exclusively caused by toxic products has been falsely maintained, especially by the German school.

Lately, however, these views have changed. The doctrine of auto-intoxication from the retention of indifferent substances has already become firmly established. At least it has been recognised by many authorities, such as A. Gautier, Bouchard, Alb. Robin, Raymond, L. Brunton, Senator, v.

§ 24. Imperfect removal of the products of retrogressive metabolism from the tissues is the cause of the auto-intoxications

§ 25. Auto-intoxications from toxic products of metabolism as neurin, cholin, etc.

§ 26. Auto-intoxication from indifferent products of metabolism, as uric acid, etc.

Leyden, L. Popoff, L. Berthenson, G. L. Hirsch, and many others, as appears from the long list of authors who have engaged in observations in the sphere of organotherapy (*cf.* the clinical part of our work). Some authors, acting on these views, attribute toxic qualities even to indifferent substances: that uric acid can produce necrosis is explained in this manner.

§ 27. The processes of oxidation of the textural respiration form the self-protection of the organism against retention of the products of metabolism

Still, the view which holds that some auto-intoxications appear as result of the accumulation in the organism, not only of poisonous, but also of indifferent substances, has so far not obtained full credence in the practice of medicine. It is, however, defended by many authorities. A clear understanding of the pathogenesis of different auto-intoxications is necessary for the explanation of the fundamental features of Organotherapy.

A weapon for the self-protection of the organism against the accumulation and retention of products of metabolism is furnished by the processes of oxidation. In fact the nitrogenous products of metabolism oxidise comparatively easily. As products of retrogressive metamorphosis they change to compounds of great solubility and diffusibility, while those which have toxic qualities lose their toxicity by means of the oxidation (Bouchard,²⁷ Gautier,²⁸ Poehl²⁹).

We have already called attention to the fact that in the external coat of the cell processes of oxidation and hydration are going on, the object of which is the removal from the cell of substances that are toxic and not readily soluble.

The activity in this part of the cell constitutes the textural respiration which is divided in the processes of oxidation and excretion. These two functions are very closely connected.

As we shall see later, this activity of the textural respiration depends under normal conditions on the degree of the alkalescency of the juices of the body, and on the presence of several enzymes, or katalysators, one of which, *Spermin*, promotes the processes of oxidation, while others, like *cerebrin* and *thyroidin*, promote the processes of excretion.

§ 28. Oxidation produces in the organism not only warmth but also osmotic pressure

Before entering in detail into the functions of these enzymes, we have yet to consider in general outline one of the phenomena of the cellular and textural life.

Formerly it was assumed that oxidation produces in the organism only one force in the shape of heat which is measured with calories. Such a one-sided opinion had received physi-

ological sanction. Prof. Poehl³⁰ had already demonstrated (in 1899) that the processes of oxidation form in the organism not only a source for the production of heat, but that they simultaneously generate a kinetical force as osmotic pressure which is measured by atmospheric pressure.

As the osmotic pressure depends on the molecular concentration, a solution containing a substance of high molecular weight—as, for instance, a one-per-cent. solution of sugar—will exercise much less osmotic pressure than an equal solution of NaCl, because the molecular weight of sugar is larger than that of NaCl. Besides, the osmotic pressure of NaCl is still further increased by this solution being liable to disintegration. Consequently there exists first an inverse proportion between the osmotic qualities of the soluble substances and their molecular weight; and secondly, the dissociability has a distinct duty to perform.

From the foregoing it appears that bodies of great molecular weight have comparatively few osmotic properties. The molecule of albumen, which has an enormous molecular weight (according to Schichkoff more than 30,000), presents hardly any osmotic qualities. In oxidation and hydration an immense number of molecules of small molecular weight (Urea = 60) are formed from the molecule of albumen, and the osmotic pressure is thus increased many thousands of times.

Therefore textural respiration, as Prof. Poehl first demonstrated, is a source for the generation of a great power, which makes itself known by a great increase of the osmotic tension. Such a tension must exist between the inner part of the cell and the juices in which it is immersed.

In every vegetable and animal cell the osmotic presence during life plays a very important part. The life of the cell can only exist so long as the osmotic tension remains in it, that is, the difference is the osmotic pressure of its parts and the surrounding medium. The communication between nucleus and protoplasm is apparently brought about by means of this osmosis.

All the cells of our organism are permeable by water; some, however, only in one direction. In consequence of the osmotic tension a constant movement of the water and the diffusible components between cells and the surrounding

fluids originates in the organism. Every disturbance of the osmotic pressure in any place causes a corresponding change of the osmotic tension in other parts of the body. An absolute equilibrium of the osmotic pressure in the organism occurs only on the cessation of all the vital functions of the cells. What has been said sufficiently explains the significance of the osmotic phenomena in the organism.

From this it appears that textural respiration performs an important function in the phenomenon of the osmotic pressure in the juices of the organism. In this connection we have to consider another factor.

§ 29. Electric conductivity depends partly on oxidation

We have already called attention to the fact that the osmotic pressure depends on the molecular concentration of the solution. In doing this, we did not consider the very important circumstance that the phenomenon of the solution of chemical compounds often goes hand in hand with the dissociation of the dissolved compounds. These molecules, which are decomposed under the influence of the solving fluid, are named ions. It appears that these ions have the faculty of playing the part of electrolytes, that is, they possess electric conductivity. Of course, the osmotic pressure increases considerably as soon as the dissolved molecules undergo a dissociation by which the relative molecular concentration is increased. Consequently the dissociation causes an increase of the molecular pressure. Simultaneously also the relative electric conductivity of the solution or the juices of the body increases. This circumstance may play an important part in the functions of the organisms. Unfortunately, however, in the investigation of the etiology of the diseases and in the discussion of their therapeutic effects sufficient attention has not, so far, been given to this matter. As we shall see later, as a consequence of the diminished textural respiration, several auto-intoxications distinguish themselves, not only by decrease of the osmotic tension, but also by decrease of the electric conductivity of the juices (Poehl³¹). In some forms of epilepsy these factors have no inconsiderable share. If we take this point of view the effect of the treatment with bromine is comprehensible (Poehl). The same point of view will also enable us to understand the unsuitability of bromine in certain cases.

§ 30. Katalysators

For the better understanding of the action of the organo-

preparations we will now turn to the question of katalysis and katalysators. (positive and negative)

From what has been already said we know that a series of chemical reactions occur both inside and outside our organism in which the presence of an extremely small quantity of a substance accelerates a reaction, and causes the change of a great quantity of another substance, or, on the contrary, checks the reaction materially. In 1894 Ostwald³² demonstrated that all similar contact-actions consist of a katalytic acceleration or retardation of the reactions.

Those substances which accelerate a slow reaction are named positive katalysators, and those which cause a retardation are called negative katalysators. As the only question here is a change of the length of time of the reactions which take place, these phenomena, as Ostwald remarks, lose a great part of the unexpectedness which, at first sight, seems to belong to them.

Ostwald calls attention to the fact that, of necessity, the katalysators have a very large share in our organism.

So, for instance, says Ostwald, "occurs the fundamental vital activity, the conveyance of the necessary chemical energy by combustion at the expense of the oxygen of the air, under the deciding co-operation of katalysators (enzymes), which would be impossible without them. For free oxygen, as is well known, is a very inactive substance at the temperature of the organisms, and without acceleration of the quickness of its reaction, the preservation of life would be impossible."

§ 31. The processes of oxidation at the expense of the oxygen of the air are feasible only under co-operation of katalysators

Let us distinguish between general and specific katalysation. The former display their activity in all the tissues and organs in which processes of oxidation and reduction take place. The specific katalysators, on the contrary, influence only certain processes occurring in certain organs. Here belong, as we shall see later, *cerebrin*, *thyrcoidin*, *pepsin*, *trypsin*, etc.

§ 32. General and specific katalysators

Prof. Poehl³³ endeavours to explain the particular character of the action of specific katalysators in the following manner : By more recent investigations the so-called semipermeability has been demonstrated, viz., that different tissues and cells have the exclusive faculty of letting certain substances pass through their membranes. For instance, urea, antipyrin, and similar substances easily enter into the erythrocytes, as

Hamburger,³⁴ Koeppe,³⁵ and others have demonstrated, while other substance do not possess this faculty. Koeppe points out that the study of this quality of semipermeability of cells constitutes one of the most important objects of physiology. As the substances forming the chief part of the organo-therapeutic preparations are gained from comminuted cells, and belong to these cells, one might suppose *à priori* that these substances have the faculty of penetrating the respective cells and tissues. In this way Prof. Poehl accounts for the elective action of the specific katalysators of organo-therapeutic preparations.

To the group of the general katalysators belong *Spermin* and *Adrenal*. The former is a positive katalysator for the processes of oxidation, the latter for those of reduction.

The first impression on the mind would be that these two katalysators are chemical antagonists, as they accelerate two opposite chemical processes. It has been demonstrated, however, by the laboratory experiments made by Prof. Poehl, that pure *Adrenal* does not interfere with the action of *Spermin*, and vice versa. This fact agrees with the theory of the katalysators and is perfectly consonant with the processes taking place in the organism. In relation to any one chemical process, however, the negative katalysator is antagonistic to the positive one. This is shown by the experiments of Prof. Prince Tarchanoff³⁶ on animals in general and on light-giving bacteria especially, from which it appears that chloroform, carbon oxide, and cyan-compounds prove to be negative katalysators of the intra-organic oxidation and are therefore antagonistic to *Spermin*, that is, to the positive katalysator of the physiological processes of oxidation.

§ 33. *Spermin*, a positive katalysator of processes of oxidation

As Prof. Poehl³⁷ has demonstrated, *Spermin* is a positive katalysator for the physiological processes of oxidation. As early as 1891 he had carefully noted the influence of *Spermin* on the processes of oxidation, and in his communication to the Imperial Academy of Sciences at St. Petersburg in 1902 (Supplement to vol. lxxi. No. 2) he said (p. 2) : "*Spermin* influences the quickness (energy) of the reaction, as can be seen by the quantity of hydrogen separated in a certain space of time."

In his book "Die physiologisch-chemischen Grundlagen der Spermintheorie nebst Klinischen Material zur therapeu-

tischen Verwendung des Sperminum-Poehl," Prof. Poehl says as follows (see page 21) :

"The duration of the reaction is shorter. *Spermin* seems to operate here in a katalytic manner, as on one side the reaction does not depend on the quantity of *Spermin*, and on the other, as appears from the following experiment, the *Spermin* remains apparently unchanged after the reaction."

The katalytic action of *Spermin* in processes of oxidation has been demonstrated by Prof. v. Poehl in a series of laboratory experiments. A similar result appears from the experiments on animals by Prof. Prince Tarchanoff, Prof. Loewy, and Richter, as well as from a large number of clinical observations in the therapeutic employment of *Sperminum-Poehl* on sick persons.

Spermin is one of the positive katalysators of the processes of oxidation in our organism. Prof. Poehl declares that he is far from making the assertion that in the organism only one positive katalysator of the processes of oxidation exist; the hæmoglobin acts in the same way. Still Poehl, on the strength of his comparative investigation, maintains that *Spermin*, which is a normal division-product of the leucocytes, takes undoubtedly the greatest share as oxidation-katalysator. His assertion, which he made ten years ago—viz., that *Spermin* is the ferment (otherwise enzyme) of the one function of the textural respiration, i.e., the intraorganic oxidation—can be maintained by him to its full extent on the ground of all his recent observations. Modern views lead us only to the conclusion that the work of *Spermin* is not limited to the textural respiration, but applies to all the processes of oxidation in the organism, including the oxidation of the outer respiration (pulmonary respiration).

In pulmonary respiration hæmoglobin also plays an important part as katalysator of the processes of oxidation. There is, however, no reason why *Spermin* should be excluded.

As already mentioned, at the temperature of the body the oxygen can oxidise but feebly, and therefore the oxidation, in the lungs as well as in the tissues, cannot possibly, as Ostwald remarks, take place without the co-operation of a katalysator. The processes of oxidation in the organism are useful to its economy only during a katalytic acceleration of their reaction. *Spermin* exerts its katalytic force in the

pulmonary, as well as in the textural, respiration, because in both cases all the necessary conditions are fulfilled.

This provides us with an explanation as to why the processes of oxidation going on in the organism at the expense of the oxygen of the air—which, like all gas-reactions, distinguish themselves at a common temperature by great tardiness—take so energetic a course in our organism. The credit for this belongs to *Spermin*, *hæmoglobin*, and different oxydases (N. O. Sieber and E. O. Schumowa-Simonowskaja³⁸).

Many observations have been made concerning *Spermin*, from which we may calculate how extremely small a portion is required to produce the requisite reaction. Ostwald lays special emphasis on the fact that the katalysators exercise their influence in very small, though always measurable, quantities.

Observations by the sick-bed show that in cases of impaired textural respiration as in cholera, scurvy, and so on, the introduction of 1 c.c. of a two-per-cent. solution of *Spermin* (one ampulla of *Sperminum-Poehl*, *pro injectione*) is sufficient to obtain the required therapeutic effect. Consequently for the acceleration of the processes of oxidation 0.02 *Spermin* (*Sperminum-Poehl*) per 75 kilos of body weight are necessary, that is for every kilo 0.00029 gm. or 0.000026 per cent.

As *Spermin* forms a normal constituent of the healthy organism, its influence can be demonstrated in those cases only when the textural respiration is decreased for any reason, because the normal organism does not need the introduction of a katalysator.

From experiments made by Prof. Poehl outside of the organism, it appears that in a diluted solution of chloride of copper the presence of a milligramme of *Spermin* suffices to cause the oxidation of a very great quantity of metallic magnesium (powdered) in a few seconds. In the same way a few milligrammes of *Spermin* suffice to restore to a large degree the lost faculty of developing the normal process of oxidation (as, for instance, of oxidising benzaldehyde to benzoic acid, or salicylaldehyde to salicylic acid). In all these reactions, the only question is an acceleration of the course of the reaction under the influence of *Spermin*.

§ 34. Adrenal,
a positive
katalysator
of the process
of reduction

We have recently discovered another physiological katalysator, which, for its novelty as well as its extraordinary energy, is of unusual interest. This katalysator is *Adrenal*—one of

the most essential active constituents of the suprarenal glands. *Adrenal* has the formula $C_{10}H_{15}NO_4$.

The characteristic faculty of this substance is that of influencing processes of reduction in an accelerating and therefore catalytic manner. As we shall see, this body has an influence on processes of reduction in such small quantities that we cannot help regarding it as a positive katalysator of the processes of reduction (Poehl³⁹).

In fact in fractions of a milligramme it is capable of reducing large quantities of potassium ferricyanide without being itself destroyed. We shall be still more convinced that we have to deal with a katalysator when we consider the physiological action of this compound.

So after Purinton,⁴⁰ an increase of the blood-pressure is obtained by 0.000024 *adrenal*, after Moore,⁴¹ even by 0.000000245 grms. per kilo of the weight of the dog.

The reducing faculties of *adrenal* are so great that Poehl⁴² employed it for the development of photographs.

In several severe cases of neurasthenia and other nervous diseases, Prof. Poehl⁴³ convinced himself of the power of the urine to develop photographic plates. He explains this as owing to the presence of *adrenal* and similar substances in the urine.

To the specific katalysators belong *cerebrin*, *thyroidin*, *hypophysin*, *mammin*, *ovarin*, etc.

Of these preparations we shall for the present deal only with *Cerebrin* (*Cerebrinum-Poehl*), because its influence on the metabolism has been very thoroughly investigated.

Besides dealing with Spermin as a katalysator of the processes of oxidation in textural respiration, we have also to consider other katalysators which, without influencing the oxidation directly, exercise their influence on the excretion of the products of metabolism from the tissues.

It appears, in fact, that in *cerebrin* (*Cerebrinum-Poehl*), which represents the synergetic group of the active constituents of the nervous substance, a positive katalysator is contained which, in very small quantities, influences the decreased excretion of the products of the textural respiration and can remove an accumulation of them (Poehl⁴⁴). In certain pathological conditions, as, for instance, in several forms of neurasthenia, epilepsy, and alcoholism, *cerebrin*

§ 35. Specific
katalysators
cerebrin,
thyroidin,
mammin, etc.

produces an effect in quantities of milligrammes. Doubtless we have in *cerebriu* a specific katalysator of the excretion of the textural respiration.

When we speak of a specific katalysator, we do not mean a medicinal specific. We mean such a body as Ostwald calls a specific enzyme. The question is, what influence has it on a specific physiological function? In this case *cerebrin* accelerates a function of the textural respiration—namely, the excretion.

As the excretion of the products of metabolism from the tissues is decreased in different diseases, the therapeutic usefulness of such a katalysator is, of course, incalculable.

In this way it may also be explained that *Cerebrinum-Poehl* has been used with success in the treatment of certain forms of neurasthenia, epilepsy, alcoholism, etc. (Lion,⁴⁵ Prof. Stange,⁶⁴ Prof. A. Eulenburg,⁴⁷ and others).

§ 36. Negative katalysators.
Toxine.

When we consider the work and significance of such katalysators, as *spermin*, *cerebriu*, *adrenal*, and others of like kind, and consider those katalysators which have long since been therapeutically employed, as *hæmoglobiin*, *pepsin*, *trypsin*, and others, we cannot help coming to the conclusion that Nature has equipped our organism liberally with katalysators. Besides the positive katalysators we have also to deal with negative ones. To the latter apparently belong, besides others, many toxins (N. O. Sieber and E. O. Schumowa-Simanowskaja⁴⁸).

Undoubtedly the study of the qualities of the positive, as well as the negative, katalysators forms one of the main objects of the medicine of to-day, and the study of the activity of the katalysators furnishes us with the means of combating the effects of the toxins.

The katalysators which are gained from the healthy organism are especially intended to influence the metabolism and make it normal, a point which the eminent Russian clinician, Prof. E. v. Eichwald,⁴⁹ has very properly recognised. In his "General Therapeutics," he says in the chapter, "Doctrine of the Natural Healing" (*Therapeutica naturæ*), quite explicitly (p. 15): "The *Vis medicatrix naturæ* of the ancients is evidently nothing but the metabolism of our body." Similarly the well-known physician to his Majesty the Czar, Dr. G. v. Hirsch,⁵⁰ recognised "in *Spermin* that substance which will bring appreciation to the *Vis medicatrix naturæ*."

Twelve years ago Prof. v. Poehl⁵¹ expressed the idea that in certain glands and organs we have house-dispensaries with an abundant stock of remedies which the organism makes use of in self-cure and in the battle with pathogenic factors. The study of the physiological and chemical qualities of the isolated protective means of the organism is not alone of high interest for biology; it has at the same time an enormous practical value, for it furnishes us with a series of active remedies for the relief of suffering humanity. And as in this case we but imitate Nature, we may feel assured that we are on the right road.

The establishment of a rational Organotherapy became feasible only after physiological chemistry on the basis of modern urinalysis had elaborated some methods of testing anomalies of the metabolism. As long as the urinalysis confined itself to ascertaining the presence or absence of a pathological constituent and the quantity of this or that constituent in the quantity of urine secreted in twenty-four hours, it was of little use for the discussion of many processes of the metabolism. To gain an idea, even approximately only, of several anomalies of the metabolism, one great obstacle had to be overcome in the exact determination of the balance of the metabolism, *i.e.*, the import and export of *n* in the organism. Since the introduction in the urinalysis of the so-called coefficients of urine (Zuelzer,⁵² Poehl,⁵³ A. Robin,⁵⁴ Bouchard⁵⁵), urosemiology and urosemiotics made rapid progress, and the great obstacle, which adhered to the quantitative determination of the import and export in the patients, has been overcome.

Already in 1882 Prof. Poehl, on patients from the clinic of Prof. Eichwald, made the first observations as to the determination of the energy of the processes of oxidation in the organism from the proportion between the nitrogen contained in urea and the whole amount of nitrogen in the urine.

As this coefficient plays an important part in the question of the employment of Organotherapy and may even serve for the estimation of the therapeutic effect, we desire to consider it still further.

A great part of the nitrogenous products of the retrogressive metamorphosis changes through oxidation and hydration to

§ 37. Urosemiotin and its significance for organotherapy

§ 38 Coefficient of urine of the energy of the processes of oxidation in the organism

urea and ammonia. The main part of the nitrogen in albumen is secreted as urea. According to Neumeister,⁵⁶ by far the greatest part of the *n* of the albuminous bodies in all animals leaves the organs in the shape of lactate of ammonium, which in small quantities is conveyed to the liver continuously, to be oxidised there to carbonate of ammonium. From the latter, through a synthetical process in the liver-cells of the mammalia, urea is formed (*cf.* v. Schroeder⁵⁷).

Therefore, although not all the urea originates directly by oxidation from the albumen, the former view that the urea, as the normal final product of the decomposition of the albuminous bodies, represents the highest stage of oxidation of the nitrogenous products of the retrogressive metamorphosis, is perfectly justified. For, although the synthetical process certainly plays an important part in the formation of urea, this formation is made possible only by the processes of oxidation in the tissues. Consequently the formation of urea depends on the processes of oxidation and can be used as indicative of the intensity of the processes of oxidation in the tissues (the intraorganic oxidation of the textural respiration). The larger the quantity of the nitrogenous intermediary products of the retrogressive metamorphosis (leucomaines) is in the urine in proportion to the quantity of the urea, the smaller is the intensity of the processes of oxidation in the organism.

This train of thought caused Prof. A. v. Poehl in 1882 to recognise in the proportion of the nitrogen of the urea to the whole amount of nitrogen in the urine a gauge as to the energy of the processes of oxidation in the organism. At that time (and unfortunately still to-day in many clinics) the customary method of determining the urea by trituration with nitrate of mercury after Liebig failed to answer the purpose, was not the real amount of urea ascertained by its means but urea plus a large part of the intermediary products. To this defect of the method Liebig himself called attention, and later on Parkes, Wollowicz, Schenk, Fick, Wislicenus, Voit, Hoppe-Seyler, and others*, but nevertheless this method is, thanks to its easy performance, still in use in many clinics.

* Hoppe-Seyler says, for instance, "As by the nitrate of mercury, besides urea, also most of the other nitrogenous constituents of the urine are precipitated, this trituration furnishes a determination of the whole nitrogen of the urine rather than a pure determination of the urea."

It stands to reason that a reagent, such as nitrate of mercury, which precipitates the urea simultaneously with the xanthin and kreatin compounds, cannot be used to make a quantitative separation of the urea from these bodies.

Therefore Prof. Pœhl tried to avoid this fault by precipitating the leucomaines (the intermediary nitrogenous products) with phosphotungstic acid in presence of hydrochloric acid before the determination of the urea (by NaBrO). The detail of this method will be given later.

In several hundred analyses of urines from patients in the clinics of Prof. Eichwald, which Prof. Poehl has made since 1882 the proportion of the urea-nitrogen to all nitrogen proved itself a good gauge of the energy of the processes of oxidation in the organism, and he gave in his analyses to this coefficient the name "Coefficient of oxidation." In 1887 Poehl⁵⁸, relying on a very great number of tests, made to the Association of Naturalists at Wiesbaden the communication that the urine of syphilitic persons distinguishes itself by a lowered coefficient of oxidation. Furthermore he has demonstrated that this coefficient changes very little in the same person, if the condition of the health remains unchanged. The variations do not exceed in such a case one-tenth per cent. In re-convalescence the coefficient of oxidation rises in accordance with the improvement of the health. In some cases of anæmia after a longer sojourn in good air, as well as under the influence of the employment of *Sperminum-Poehl*, the coefficient of oxidation of the urine was found materially increased. Diseases which accompany decreased oxidation caused a rapid lowering of this coefficient.

Now, after Prof. Poehl has determined this coefficient in many thousands of cases within the last twenty years, he can, on the foundation of this material, make the assertion that this coefficient furnishes us with a very exact diagnostic means of estimating the processes of oxidation in general and the textural respiration especially. Prof. Poehl therefore states expressly⁶⁰ that the subjective "bien être général" finds an objective clinical expression in this coefficient.

Unfortunately many clinicians still value only the absolute determinations of the urine, and many believe that an insight

into the metabolism of the organism is afforded only by an exact determination of the daily introduction and excretion of *n*. The erroneous supposition is also made that all the nitrogen which is found in the excrements had not been in circulation (Hermann). In his thorough koprological investigations v. Oefele⁶¹ has shown that the fæces of a healthy person under normal conditions originate for the greater part in the bowels and consist of undigested food only in an infinitesimal degree.

Careful observations of the metabolism carried on for a long time on an organism which has been regulated to the equilibrium of nitrogen, have doubtless a great scientific value. It is, however, difficult to perform such observations on sick persons. Neither do they supply us with the knowledge which we obtain by means of the relative values, the coefficients. The urine, which is properly called the looking-glass of the metabolism, must show to the clinician the present condition of the metabolism of the patient. For his judgment of these over a longer period careful observations serve the purpose best.

Independently of Prof. Poehl, Prof. Alb. Robin⁶² in 1886 enunciated the proportion of the urea to the total amount of the dissolved solid constituents of the urine as an approximate expression of the processes of oxidation. Robin adds, "this coefficient is very variable according to the individuals and the pathological circumstances. In one subject, however, regular dieting being maintained, it suffices for all clinical requirements." (*Ce coefficient est très variable, suivant les individus et les circonstances pathologiques; mais chez un même sujet, avec une alimentation identique, il suffit aux besoins de la clinique.*)

Alb. Robin⁶³ accounts for the proportion between the total nitrogen in the urine and the nitrogen of the urea as the coefficient of oxidation as follows: "Comme l'urée est le produit le plus parfait de l'oxydation des albuminoïdes, le rapport qu' affecte l'azote de cette urée avec l'azote total de l'urine, pourrait servir à chiffrer les taux des oxydations élémentaires et être dénommé à ce titre: coefficient de l'oxydation."

In Germany and England the employment of the coefficient has so far found but few friends, although v. Noorden gives

the demonstration of the intermediary products of metabolism in the urine as a means of ascertaining the decrease of the oxidation in the tissues of dyspnoeic persons, in default, as he says, of any exact experiments on the respiration.

R. Hugnet⁶⁵ has also experimented with the "Coëfficient d'oxydation" of Robin, which he calls "coëfficient d'utilisation de la machine humaine."

Bayrac⁶⁶ in his dissertation calls it "rapport azoturique."

Bouchard⁶⁷ formerly employed for clinical purposes the proportion between the total amount of solid constituents in the urine and the urea. (Coëfficient de Bouchard.)

Now, however, Bouchard,⁶⁸ as well as Gley, Ch. Richet, Ritter, Thorion, Moreigne, and others use the coefficient introduced by Poehl in 1882, and later also by Alb. Robin, *i.e.*, that of the urea-nitrogen to the whole nitrogen of the urine. Based on about 7000 quantitative urinalyses, made in the manner to be described later, Prof. Poehl established the following rules :

During a normal energy of oxidation the proportion of urea-nitrogen to the total nitrogen varies in man between 91 : 100 and 94 : 100. Under very favourable circumstances even the coefficient 96 : 100 has been noted. The coefficient below 91 indicates decreased processes of oxidation. From 91 : 100 to 87 : 100 the oxidation is moderately decreased, below 87 it is considerably so. The amount may fall below 60. In a case of Asiatic cholera Prof. Poehl has observed an amount as low as 47.8. According to E. Pflüger and K. Bohland⁶⁹ the proportion between the whole nitrogen of the urine and the urea-nitrogen averages 100 : 89.

It will appear strange that in fever the processes of oxidation are decreased. Prof. Poehl, however, shows that this is so. In fever a large quantity of albuminous substances in the body are decomposed, and the absolute amounts, even of urea, are large. The relative formation of urea, however, is small, and the relative quantity of the intermediary nitrogenous products of metabolism (leucomaines) is great. This view, however, is not held by Prof. Poehl alone. Relying on the determination of the coefficient of oxidation, Prof. A. Robin truly says that in typhoid fever the processes of oxidation are diminished (*dans la fièvre typhoïde les oxydations sont diminuées*).⁷⁰ In determinations of the urea after the method

of Liebig, and even when observing the improvement of this method by Pflueger, earlier writers invariably found in feverish persons a very great quantity of urea. The explanation is that during fever some intermediary products are found in the urine in increased quantities, *e.g.*, kreatinin (Munck, Hofman, Lehmann, Griesinger, Schotten), hypoxanthin (Pouchet), xanthin (Pouchet), and uric acid. Seeing that as already mentioned, the xanthin- and kreatin-compounds are precipitated by nitrate of mercury simultaneously with the urea, an idea obtained credence, but was altogether erroneous, that during fever the formation of urea and the decomposition of albuminous bodies are increased. Instead of this, during fever the decomposition of albuminous bodies is great, as well as the formation of the intermediary products; but the intensity of the processes of oxidation is decreased.

For the determination of the co-efficient of oxidation Prof. Poehl uses the following method :

§ 39. The
determina-
tion of
Poehl's co-
efficient of
oxidation

The total amount of the nitrogen in the urine is determined as follows : To 100 ccm. of the urine free from albumen 25 ccm. of muriatic acid (specific gravity = 1.124) are added, besides 15 ccm. of water and 10 ccm. of phospho-tungstic acid (prepared according to directions to be given later). In the filtrate, which is to the original urine like 1.5 : 1, the nitrogen is determined with BrNaO (respectively a mixture of 5 parts of a solution of caustic soda (1 : 2) with 1 part of bromine). The total of the nitrogen is determined after Kjeldahl-Henniger. The urine is treated with sulphuric acid in presence of phosphoric acid. To 25 ccm. of urine 5-10 ccm. of a mixture of 10 parts of concentrated sulphuric acid (1.84) with 1 part of phosphoric acid-anhydride is added and for twelve hours heated until it is perfectly discoloured. The contents of the bottle are then diluted with water until 100 ccm. 4 ccm. of this solution, corresponding to ccm. of the original urine, are placed in Yoon's apparatus and neutralised with caustic soda over mercury (to avoid loss of ammonia). Then the freshly prepared mixture of 20 parts natron-lie (1 : 2) with 1 part of bromine is poured in and the quantity of *n* now separated is determined the known precautions being carefully taken. It is to be noticed here, that together with the nitrogen of the urea that of the ammonia is also determined. This fault of the method, however, does not affect the determination of the energy of the oxidation, because NH_3 also belongs to the products of the physiological oxidation.

As there are different phospho-tungstic acids, and in the trade one is often given which precipitates (?) urea, it is wisest to prepare one's own phospho-tungstic acid after the following directions : 105 parts of tungstate of soda are boiled with 350 parts of water and 105 parts of phosphoric acid (specific gravity 1.15) and after cooling 25 parts of muriatic acid (specific gravity 1.124) are added. This phospho-tungstic acid is equal to all the requirements for the precipitation of the leukomaines out of the urine in presence of muriatic acid (Poehl⁷¹). The precipitation of the phospho tungstate occurs early in presence of muriatic acid. A more exact determination of it

is obtained, after the determination of the amount of n by treatment with H_2SO_4 and $NaBrO$ (Poehl⁷²).

In this method the n of the ammonia is ascertained together with that of the urea. In judging the intraorganic oxidation the n of the ammonia need not be separated from that of the urea, as the ammonia corresponds to a higher grade of oxidation than the other intermediary compounds, and therefore stands in this respect nearest to the urea.

The method is not free from objections, as Prof. Poehl has several times stated. He still uses it, however, and for the following reasons, viz., (1) because it furnishes constant results, and (2) it is easily performed (therefore feasible in clinics).

As we had already seen, the processes of oxidation depend on the alkalinity of the juices. For the control of the organo-therapeutic effects the determination of the alkalinity of the juices has great significance.

To ascertain a decreased alkalinity of the juices we employ the proportion between the total of the phosphoric acid of the urine and the quantity of phosphoric acid which it contains as phosphate of soda.

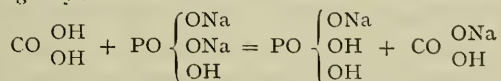
§ 40. Coefficient of urine for the determination of the alkalinity of the juices

As the quantity of phosphate of soda in the urine (in absence of fermentation in the bladder) must depend on the alkalinity of the juices, and the relative increase of the phosphate of soda can under such circumstances, according to Prof. Poehl, take place only by an increase of the alkalinity of the juices, Prof. Poehl ascertains in urinalysis the proportion between the phosphoric acid of the phosphate of soda and the total of phosphoric acid in the urine.

The determination of the phosphate of soda is made after the method of Freund.

The blood reacts alkaline on litmus-paper. However, as it contains bicarbonates, it can, as Maly remarks, from a chemical point of view be considered as acid.

Neumeister⁷³ explains the rôle of CO_2 in the formation of the acid urine in the following way :



The alkaline sodium phosphate is changed to the acid monosodium phosphate, which is passed over to the urine. The alkaline bicarbonate of sodium remains in the blood. Prof. Poehl⁷⁴ has made a long series of experiments to test the influence of carbonic acid, uric acid, and lactic acid on a mixture of dissolved monosodium and disodium phosphate.

The coefficient of urine of the alkalinity of the blood suggested by Prof. Poehl cannot be considered in every case

as a direct expression of the alkalinity of the blood. According to Prof. Poehl its decrease does not always correspond with the decrease in the alkalinity of the blood, as in case of an increased excretion of acid from the organism the decrease of the coefficient need not always be proportionate to the decrease in the alkalinity of the blood. From the experiments of Hinteregger,⁷⁵ it appears that the acids usually diosmote quicker than the acid salts and the latter quicker than the neutral salts. Experiments with sulphuric acid, bisulphate of potassium, neutral and acid oxalate of potassium, monosodium, and disodium phosphate have proved this.

This law partly accounts for the way in which the organism gets rid of the soluble and acid compounds which are not further oxidisable. Therefore the lowered coefficient of alkalinity of the urine during an increased secretion of acid from the organism need not always keep pace with a proportionately decreased alkalinity of the blood. Hence Prof. Poehl considers his urine-coefficient of the alkalinity of the blood, if judiciously used, a very useful criterion for clinical purposes. Under normal conditions Poehl has found that the proportion between the total phosphoric acid and the phosphate of soda equals 100:40. The absolute values which OH^{76} found agrees well herewith.

In the clinics of Prof. von Leyden observations have recently been made by Hausmann⁷⁷ on the excretion of acid in the human urine under physiological conditions. Here a coefficient is computed from the proportion between the total phosphoric acid of the urine and the monosodium phosphate. For reasons given above this coefficient is quite as useful as that suggested by Prof. Poehl. It has, however, the disadvantage that the proportion is not direct, but inverted. The observations are indeed very interesting. Hausmann recommends his method of testing for judging the alkalinity of the blood. Tonlie⁷⁸ also claims that the acidity of the urine can be considered as a gauge for the decreased alkalinity or increased acidity of the blood.

Bouchard⁷⁹ called attention to the fact, and with good reason, that the acidity of the juices is chiefly caused by organic acids, namely, lactic acid. The influence of the acid is not paralysed by neutralisation but by its destruction in the organism through processes of oxidation. The acidity of the juices is

called by Bouchard "l'oxydation imparfaite des acides organiques."

Consequently this coefficient of the alkalinity of the blood depends on the energy of the processes of oxidation, as is shown by the investigations of Senator, Loewy, Richter⁸⁰, and Poehl.

A materially increased secretion of acid has been observed by Poehl during the convalescent period after some severe cases of infectious diseases, *e.g.*, diphtheria, croupous pneumonia, etc. Also after the use of spermin Poehl sometimes observed a decrease of the coefficient of the alkalinity of the blood. This decrease, however, occurred only temporarily, and *ceteris paribus* there was later an increase of the coefficient.

As the moments of the formation of acids in the organism are very manifold, this coefficient is also comparatively little stable. Nevertheless, it has a certain clinical significance, especially in connection with other coefficients.

Poehl has demonstrated by numerous investigations that the coefficient of the energy of the oxidation is in a manner directly proportioned to the alkalinity of the juices of the organism, that is to say, in decreased alkalinity a decrease of the energy of the oxidation occurs simultaneously. In the beginning Poehl accounted for this coincidence of facts by the passing over of *Spermin* from the active, soluble form into the inactive and not readily soluble form of the phosphate of Spermin. The fact that in different diseases with decreased textural respiration the so-called Charcot-Leyden's crystals (phosphate of Spermin) were found, should support this view.

This explanation is opposed neither to the theory nor the facts. Based on Bouchard's⁸² views already mentioned Prof. Poehl gave still another explanation of the connection between the decreased alkalinity of the juices and the decrease of the processes of oxidation in the textural respiration. The organic acids originating in the organism—especially lactic acid as a product of irritation of the nervous and muscular systems—are not destroyed if insufficiently oxidised, and therefore cause those forms of disease which are known as acidulation of the juices (Acidosis, after Prof. Senator⁸³). Further, it became apparent, that sometimes, under pathological conditions, a positive katalysator of the processes of reduction—*adrenal*—appears in the juices.

§ 41. The process of oxidation depends on the alkalinity of the juices of the organism

The presence of such a katalysator as adrenalin in the juices, naturally accounts for the decrease of the processes of oxidation of the textural respiration, that is, of the intra-organic oxidation.

Those cases in which Prof. Poehl succeeded in demonstrating the presence in noticeable quantities of bodies similar to adrenalin in the urine were always connected *de facto* with a decrease of the coefficient of alkalinity of the juices.

The passage of adrenal and of bodies similar to it from the cells into the circulation is explained by Poehl as owing to a decreased alkalinity of the juices in consequence of insufficient oxidation of the lactic acid, which originates in over-irritation, over-fatigue, etc.

Adrenal is found in different forms of auto-intoxication, as well as in some forms of neurasthenia, and can easily be discovered without urinalysis. Hence Poehl has called attention to the fact that the urine of such patients has sometimes the capability (though in small degree only) of developing photographic plates.

§ 42. Coefficients of uric acid diathesis

To a certain extent Zerner's coefficient of urine may also serve as an expression of the alkalinity of the blood, and it may therefore be used as a gauge for the processes of intra-organic oxidation. This coefficient is also considered as a gauge for the diathesis of uric acid.

Under Zerner's coefficient of urine the proportion between the quantity of uric acid and that of phosphoric acid in phosphate of soda in the urine is understood.

Zerner has recommended this coefficient for the judging of the retention of uric acid in the tissues. Under normal conditions this coefficient is as 0.2 to 0.35. A retention does not take place if the proportion of the uric acid to P_2O_5 as phosphate of soda is smaller than 0.35 or, in other words, if the total sum of the uric acid is small or the quantity of the phosphate of soda increased. This proportion, beside serving as an expression for the alkalinity of the blood, might also furnish a gauge for the excretion of uric acid in the tissues, as in decreased alkalinity of the blood only little phosphate of soda can be in the urine. The consideration of this coefficient may, even before the appearance of any manifest symptoms of gout, call attention to the existence of the uric acid diathesis.

To the connection between the acidity of the urine and the

power of excretion of uric acid attention has been called many times. (Hoppe-Seyler, Gautier, Salkowski, v. Leyden, Chevreuil, Ebstein, C. Posner, L. Berthenson, Treskin, Severin, Mordhorst, and others.)

Poehl had occasion to observe some extremely great variations of this coefficient. In a neurasthenic alcoholic with cirrhosis of the liver shortly before death a coefficient of 3.2 (?) was observed.

In the clinics of Prof. Senator the coefficient used represents the proportion of the n of the uric acid to the total of the n of the urine. This coefficient has been used by Dr. P. F. Richter⁸⁴ as well as by others for the purpose of testing the influence of *Sperminum-Poehl* on the formation of uric acid (cf. chap. v).

While Zerner used the proportion of the quantity of uric acid to that of phosphoric acid in phosphate of soda, Bouchard and Senator each independently of the other proposed a coefficient which has also great significance for the determination of the uric acid diathesis. This coefficient of Bouchard and Senator ascertains the proportion of the total of the nitrogen in the urine to that of the n of the uric acid.

This coefficient is evidently quite as useful as that of Zerner for the determination of the degree of retention of the uric acid in the tissues; for the presence of the uric acid in the urine evidently depends on the alkalinity of the juices in general, and on the relative amount of phosphate of soda especially. It is very constant, and varies under normal conditions between 1.3 and 1.6 only. As we shall see later, it was used by Senator⁸⁵ as well as others, for the demonstration of the influence of *Spermin* (*Sperminum-Poehl*) on the metabolism.

As touching the important question of the intensity of the metabolism in the nervous tissue urosemiology disposes of many important and valuable coefficients.

Long ago the neuropathologists turned their attention to the fact that the proportion between the nitrogenous compounds in the urine, and the quantity of the phosphates excreted with the urine presents great clinical interest. One of the first to do so was the Russian savant, Prof. v. Merzejewsky.⁸⁶

Zuelzer⁸⁷ was the first who, from the point of view of

§ 43. Coefficients of urine for the determination of the intensity of the metabolism in the nervous tissue

urosemiology, paid proper attention to the proportion between the total nitrogen of the urine and the quantity of phosphoric acid. He found this coefficient under normal conditions for the same person pretty constant, and about 20. It varies in different nervous diseases, its decrease pointing to the retention, and its increase to the increased excretion of the products of decomposition of the nervous tissue.

Prof. Mairet⁸⁸ and Gilles de la Tourette also called attention to the great significance of this coefficient in different affections of the brain. So Mairet⁸⁹ for instance, says: "In maniacs the quantity of phosphoric acid in all its shapes rises in the stage of excitement and falls in that of depression."

The proportion of the total quantity of phosphoric acid to the quantity of this acid in shape of earthy phosphates furnishes, according to Gilles de la Tourette, an important sign for the determination of some hysterical and neurasthenic forms. Under normal conditions the alkali-phosphates form about two-thirds of all the phosphates, so that about one-third of the total quantity of the phosphoric acid in the urine belongs to the earthy phosphates. Cathelineau and Gilles de la Tourette found that this proportion may change materially in the course of hysterical spells. The same was observed by Yvon and Gilles de la Tourette in neurasthenics.

Prof. Poehl accounts for the appearance in increased quantity of earthy phosphates in the urine by an insufficient intraorganic oxidation, and by the presence of a great quantity of lactic acid in the juices. This lactic acid, which was not oxidised in the organism, brings about the washing out of the salts of magnesia and lime.

As A. Robin first pointed out, this factor, which promotes the excretion of the salts of lime and magnesia from the organism, is a very important and ominous symptom for the patient.

According to A. Gautier, Robin, and Vieillard the proportion of the quantity of phosphoric acid to the quantity of urine furnishes a valuable coefficient for the determination of a series of diseases which find their objective expression in phosphaturia. There are two sources for the phosphor of the urine, first the phosphor of alimentary origin, and secondly, the phosphor which is the product of disassimilation of the lecithines and the nucleines. But however the phosphoric acid

be produced there is always a certain proportion (Gumblick, Vieillard,⁹⁰ Zuelzer, A. Gautier, A. Robin, Thorion, Gron) between phosphoric acid and urea, which, after A. Gautier,⁹¹ is as 1 : 10.92. According to Poehl this proportion varies during health from 1 : 10 to 13.5. Thorion takes even the proportion of 1 : 13.62 as possible.

If the total of the phosphoric acid does not exceed the rule, but the proportion grows in the sense of the excretion of phosphoric acid, we have a condition which A. Robin calls "phosphaturic relative." It indicates an increased decomposition of the organs rich in phosphor.

According to v. Eichwald, Robin, and Bouchard, the salts of lime and magnesia are of great significance in the immunity of the organism. In fact, in consumptives, in whom the so-called "mineral diabetes" has appeared, the disease has already assumed a serious course. From this time onward the organism is no more able to fight the pathogenic microbes.

§ 44. Co-efficient of demineralisation

We cannot absolutely share the opinion that the main task here belongs to the salts of lime and magnesia. A much greater importance appertains to the decrease in the alkalinity of the juices and to the disturbance of the textural respiration. As already mentioned, these conditions are caused by the accumulation of lactic acid in the organism, which is in part excreted in the form of salts of magnesia and lime, and in this way produces demineralisation.

Anyhow, these facts demonstrate the enormous significance the coefficients of the urine have to the practising physician—and this not only for the diagnosis, but also for the prognosis and the control of the therapeutic success.

The attempt to judge the vital energy from the results of the urinalysis may possibly appear strange to those who are not adepts in urosemiology.

§ 45. Co-efficient of urine for judging vital energy

However, such savants as v. Eichwald, Bouveret, Chabrié admitted the possibility of judging the dynamism of life from the results of the urinalysis. The proportion of urea to chloride of sodium will serve as coefficient for this purpose. Under normal conditions this proportion is 2 : 1.

Eichwald and Chabrié attributed to this coefficient especially a prognostic value. Formerly it was considered as important only in diseases of the lungs. Now, however, it appears that it keeps pace with the osmotic tension of the

juices. Therefore, as we shall see later, it is of the utmost importance to the practising physician.

An entirely unfounded objection was made against this coefficient, based on the assumption that by the introduction of NaCl into the food this coefficient could be influenced. Such an objection could only be made by a man who neither observed it in sick nor in healthy persons. This coefficient can be influenced in this way in healthy people, but never in a sick person. We may give to a patient with pneumonia any amount of NaCl; this coefficient, however, will not be changed in any way. The patient will be more likely to die, because the quantity of chloride in the urine does not increase, in spite of its plentiful introduction with the food.

§ 46. Co-efficient of urine from which fermentation in the bowels may be judged

After it had been demonstrated by Kuehne⁹² and Nencky⁹³ that indol is a product of putrefaction of albumen under the influence of bacteria, and by the investigations of Jaffé,⁹⁴ E. Salkowski,⁹⁵ Baumann, Brieger,⁹⁶ the fact had been established that indol forms a source for the indikan which is constantly present in the urine (indoxyl-sulphuric acid), the assumption seemed justified that the character of the fermentations in the bowels might be judged from changes to be observed in the urine.

As far as we know, Senator,⁹⁷ in 1877, was the first who drew attention to the increased amount of indikan in the urine during disturbances of the digestion from hunger or abnormal ingestion of food.

Later on the diagnostic importance of the indikan of the urine was more certainly ascertained by C. Ewald, Brieger, Ortweider, v. Miller, and v. Jaksch. It was shown that an increase in the intensity of the putrefaction in the intestines causes an increase of the amount of indikan in the urine. It was shown that owing to the processes of putrefaction of albumen taking place outside the bowels in other cavities of the body, an increased secretion of indikan was also caused. v. Jaksch, for instance, found in a case of ichorous pleuritic exudation an enormous quantity of indikan in the urine. The appearance of very large quantities of indikan co-incident with symptoms of peritonitis he considered as indication of a complication of the inflammation with a process of putrefaction.

Consequently Prof. v. Jaksch is perfectly right when pointing out that one must not directly diagnose a putrefactive abscess as the cause of an increased amount of indikan in the urine, nor must one from this symptom infer that there is only increased putrefaction in the bowels. As we shall see later, a thorough study of the qualities of the urine furnishes us with very important diagnostic data as to the character of the fermentations in the intestines.

For this purpose we have before everything else to enlighten ourselves as to the manner in which the constant constituent of the albumen—namely, the sulphur—is excreted by the kidneys and in what proportion it stands to *n*.

Only a very small part of the sulphuric acid of the urine comes from the sulphates in the food. An incomparably larger part of it is formed by the oxidation of the sulphur-containing albumen in the organism. By the formation of sulphuric acid from the albumen the prevalence of the acids over the bases which they contain is caused in the urine. Hammarsten⁹⁸ determines the quantity of sulphuric acid excreted with the urine in the course of twenty-four hours as $2.5 \text{ H}_2\text{SO}_4$. As the sulphuric acid is mainly formed from albumen, the excretion of the sulphuric acid is about equal to that of the urea. The proportion *n* : H_2SO_4 is according to Hammarsten a fairly constant one, namely 5 : 1. However, all the sulphur of the albuminous bodies does not oxidise to sulphuric acid. A small part is excreted by the kidneys in the shape of rhoden-hydrogen and thiosulphuric acid. Another (quite insignificant) part goes to the formation of other, still unknown, sulphur-compounds.

Following the suggestion of E. Salkowski⁹⁹ the sulphur constituting the "sulphuric acid-part" is named "acid-sulphur," while the balance of the sulphur to distinguish it from the former is named "neutral" or "non-oxidised" sulphur.

According to the investigations of Lépine¹⁰⁰ a part of the compounds which contain "non-oxidised" sulphur distinguishes itself by oxidisability, and is changed to sulphuric acid under the influence of chlorine or bromine, while another part, which is not so readily oxidised, *e.g.*, the taurin, passes into sulphuric acid only by separation by the aid of saltpetre (with caustic potash or soda).

Although the quantity of the neutral sulphur depends on the food, the pathological processes in the organism have an essential influence on it.

According to the statements of Salkowski, Lépine, and Stadthagen the quantity of the neutral sulphur in the urine of healthy persons is from fourteen to twenty per cent. of the total quantity of the sulphur (one-fifth of the neutral sulphur is readily oxidisable). According to Kunkel dogs with fistula of the gall-bladder give less neutral sulphur than does the normal dog (20 per cent. against 30 and 36 per cent.). However, when jaundice is produced in dogs, an increase of partially oxidised sulphur (according to Lépine up to 46 per cent.) is observed. This agrees with the fact that feeding with taurin increases the excretion of neutral sulphur (taurocarbaminic acid).

In human jaundice from different causes Lépine found 25 to 62 per cent., of neutral sulphur. The quantity of sulphur not readily oxidisable, however, was four to five times greater than the average.

In the same manner in other diseases, especially pneumonia (without icterus) the quantity of neutral sulphur (together with that not readily soluble) may be increased. In pneumonia principally the easily oxidisable part increases; while in liver diseases the increase is in the part not readily oxidisable. Reale and Velardi¹⁰² also observed the increase of the quantity of neutral sulphur in diseases of the liver.

In dogs the diversion of the gall outside causes only a small decrease of the not readily oxidisable sulphur.

Voirin¹⁰³ in his Dissertation discusses the increase of the oxidisable sulphur in infectious diseases.

Reale and Velardi¹⁰⁴ determined the total amount of the sulphur in the urine as 1.3 grm. per day. In diabetes the total amount of sulphur increases

§ 47. The different compounds of sulphur in the urine

more than in any other disease, and exceeds more than twice the normal amount, while the quantity of neutral sulphur is increased more than the quantity of the acid (60-39 per cent.). With the disappearance of the sugar from the urine the amount of the neutral sulphur largely decreases (45.6 per cent.), that of the acid sulphur, however, increases. In consideration of the high amount of sulphur in cystin (about 30 per cent.) it is easy to understand why, as Stadthagen¹⁰⁵ has observed, the amount of neutral sulphur in cystinuria increases.

The so-called "acid-sulphur," viz., sulphuric acid, appears in the urine in two forms, namely, as salts of the common sulphuric acid and as etherical sulphuric acids in union with the alcohols of phenol, indoxyl, skatol, &c.

To derive benefit from the urinalyses for diagnostic purposes, the compounds of sulphuric acid must be determined separately in the form of ethyl-sulphuric acids. The constant presence of compounds of the phenol-series in the urine was established by Städeler.¹⁰⁶ Under the most different conditions parakresol is found in human as well as in animal urine (Brieger,¹⁰⁷ Baumann,¹⁰⁸); rarely, however, and only in small quantities, are phenol, breznkatechin, and hydrochinon found in it. In human urine the whole daily quantity of parakresol and phenol, taken together, is not more than 0.03 grm. (Kessler and Penny¹⁰⁹). According to Salkowski¹¹⁰, the amount of phenol under pathological conditions is increased; according to Brieger,¹¹¹ this increase occurs, too, during constipation (especially with accumulation of fæces in the small intestines and the colon), in peritonitis, in suppurations and pyemia, and, according to Blendermann¹¹², in phosphor-poisoning. Urine rich in indikan shows at the same time an increased amount of phenol. Urine, rich in phenol, however, does not always show an increased amount of indikan.¹¹³ Poehl¹¹⁴ experimented on himself to ascertain the proportion between the amount of primary sulphuric acid and that of ethyl-sulphuric acid, and he found that this proportion was under normal conditions, 11 : 1. During an exclusive milk-diet it increased to 36 : 1 and on the use of comparatively large quantities of water of carbon disulphide (Aq. carbon. sulphurat 200 ccm., which produced severe symptoms of intoxication) the proportion rose to 38 : 1.

These observations by Poehl gave Albu¹¹⁵ occasion to recognise in a milk-diet one of the remedies for intestinal auto-intoxication.

In the clear statements of H. Hamburger¹¹⁶ and A. v. Korányi,¹¹⁷ the mutual influence of the osmotic pressure in the blood, the lymph, and the urine is thoroughly discussed. The important part played by the osmotic pressure of the juices is clearly shown, that is, the circulation of the blood and the lymph as well as the secretion and excretion of the urine.

§ 48. The significance of the physical-chemical coefficients of urine

The molecule of the albumen is a giant-molecule, which is capable of soaking only not of solution. Therefore the albumen, as such, has no influence on the osmotic qualities of the juices. The life of the cell, however, is connected with decomposition of albumen. The products of the decomposition of this giant-molecule, as far as they are soluble, must increase the osmotic qualities of the juices. As it appears from the investigations of Armand Gautier and Poehl, the solubility of the products of decomposition of albumen is in direct proportion to the energy of the processes of oxidation in the tissues. Therefore in the aërobic life of the tissues, while they are washed plentifully with oxygen-carrying blood, some readily soluble products of decomposition of albumen are formed, while during a decreased intraorganic oxidation the products of the decomposition of the albumen form some compounds that are not readily soluble. In this way it is evident that, in normal intraorganic oxidation, the life of the cell causes an increase of the osmotic pressure of the juices (Poehl¹¹⁸), while a decreased intraorganic oxidation produces a diminution in the proportions of the osmotic pressure.

The difference in the osmotic pressure which is thus produced between the fluids in the textural fissures and the contents of the lymphatic vessels causes the aspiration of fluid from the lymphatic vessels into the textural fissures. Therefore the circulation of the lymph is not caused by the pressure of the blood exclusively, but, to a great extent, by this suction of the metabolism. In continued metabolism the fluid of the textural fissures would reach so high a degree of osmotic tension that the vital activity of the cell would be unfavourably affected, and the course of the metabolism interfered with. This, as v. Korányi properly remarks, would mean the death of the cell. It is prevented by the addition of dissolved molecules, which results from the destruction of albumen and raises the osmotic pressure, being led to the kidneys by the blood and excreted.

§ 49. Kor-
ányi's coeffi-
cient of urine

According to v. Korányi,¹¹⁹ the urine contains in a given quantity of water three times as many dissolved molecules as are in a similar quantity of blood. Whence this author concludes that the kidneys decrease the whole osmotic pressure of the blood, and, in this way, contribute essentially to the maintenance of a constant difference in the osmotic pressure between blood and textural juice. From a consideration of the fact that the activity of the kidneys in removing the urine increases the difference of the osmotic pressure between the blood and the textural juice, in this way accelerating the movement of the lymphatic current, v. Korányi very properly gives to the kidneys the importance of a true lymphatic heart.

Consequently, the osmotic pressure of the excreted urine is in direct relation to the proportions of the osmotic pressure of the blood and the textural juices, as a test of which it may serve during a normal function of the kidneys.

The lowering of the freezing-point of the blood-plasma is in a healthy man $= \Delta = 0.570^{\circ}\text{C}.$; while that of the urine varies under normal conditions from 1.3 to $2.2^{\circ}\text{C}.$

v. Korányi has investigated the proportion between the value of the lowering of the freezing-point and the percentage of NaCl in the urine.

In the coefficient $\frac{\Delta}{\text{NaCl}}$ v. Korányi sees the formula for the swiftness of the current of the urine in the urinary canaliculi.

As there is a pretty constant proportion between the freezing-point and the amount of NaCl of the normal urine, this coefficient of Korányi will really serve as an expression for the movements of the urine in the urinary canaliculi of comparatively healthy people. As, however, in many diseases the amount of NaCl is subject to very great variations, and does sometimes (as, for instance, in grave cases of pneumonia) almost entirely disappear, such a coefficient of urine is, in the opinion of Prof. Poehl, not applicable to all clinical conditions, because for one reason that, even from a mathematical point of view, it is sometimes unjustifiable; for, with the diminution of the divisor the coefficient rises to infiniteness, thus:

$$\frac{a}{0} = \infty$$

In his investigations Prof. Poehl made efforts to find,

besides the absolute osmotic pressure of the urine, a value which does not depend on the concentration of the urine. The absolute osmotic pressure of the urine depends in the first place on the concentration, that is, the quantity of the dissolved molecules. It follows, therefore, that if the weight of the dissolved substances is equal, the molecules of small molecular weight exercise a comparatively higher pressure than the molecules of larger molecular weight (as, for instance, 1 gm. of NaCl contains a larger number of osmotically operating molecules than 1 gm. of NaBr., and the latter more than 1 gm. of sugar).¹²¹ Further, the water in certain dilutions has a separative influence on the molecules of salt. Therefore, in place of the molecules of salt, the corresponding ions (which in varying concentration appear in varying quantity) will exercise the osmotic pressure.

§ 50. The osmotic coefficient of urine from the investigations of Prof. v. Poehl

Poehl is convinced that to the clinician the absolute values of the osmotic tension of a urine, that is the osmotic pressure, which existed at the time the sample was taken and depended on the ingestion of liquids and other accidental circumstances, is of less interest than such data as permit an insight into the osmotic qualities of the dissolved constituents of the urine. They furnish a coefficient of urine which expresses the capability of the substances concerned to produce an osmotic tension, and this independently from the existing concentration.

Cl urine which contains, with a high specific gravity, a comparatively great quantity of urea, uric acid and xanthin-compounds besides pepton, with a small amount of chlorides (as in croupous pneumonia before the crisis) may show a high *absolute* osmotic pressure, while a urine (as we often find it in diabetes insipidus) which has a small specific gravity contains little urea and few chlorides, etc., and shows a very little lowering of the freezing-point—that is, a very small, *absolute* osmotic pressure.

When, however, we compare the osmotic qualities of the dissolved constituents of these two urines after the following method—which has been devised by Poehl—it becomes evident that the constituents of the urine in croupous pneumonia possess a *comparatively* much smaller osmotic power than those of the diabetes insipidus. Further, when we give an account of the chemical character of the urine in pneumonia,

we see the kreatin-, xanthin-, and uric-acid-groups, which have high molecular weights, represented in great quantities in proportion to the urea—and the giant-molecules of pepton are to be added. On the other hand, in diabetes insipidus the intermediary products are present in small quantity in proportion to the urea, together with a comparatively greater amount of chlorides. The molecular weights of the urea and the chloride of sodium are small in comparison with those of the uric-acid-, xanthin-, and kreatin-groups.

Consequently a certain weight of the dissolved constituents of the urine in pneumonia possesses a smaller quantity of molecules than the same weight of dissolved constituents of the urine in diabetes insipidus. Therefore the *relative* osmotic qualities of the urine in pneumonia must be smaller than those in diabetes insipidus. To this conclusion we are also led by the method proposed by Poehl¹²² of determining the “facultative osmotic values” or “osmotic coefficients of urine,” and this result agrees perfectly with what is going on in the organism in pneumonia and in diabetes insipidus. As proof we need only point to the enormous difference between the amount of urine passed daily in both cases.

For the purpose, therefore, of obtaining such values as can be compared one with another, and to characterise the faculty possessed by the dissolved constituents of the urine of exercising the osmotic pressure, that is the facultative osmotic pressure, Prof. Poehl has proceeded as follows :

He found it best to bring out the absolute osmotic tension of the animal fluids in atmospheric pressure. The lowering of the freezing-point of the urine (Δ) being ascertained, the absolute osmotic pressure of the urine is computed in atmospheres after the formula $P_a = 12.07 \Delta$.

To make this value, independently of the immediate concentration, comparable with other statements, Poehl considers it as a cent. per cent. solution of the respective constituents of the urine. For this purpose either the dry residue of the urine is determined by evaporation (the necessary precautions being taken) or the residue R (expressed in per-cents.) is computed after the formula $R = 233 (D - 1)$, D being the specific gravity.

The facultative osmotic value of a respective cent. per cent. solution which we will mark, like Poehl's osmotic coefficient

of urine, with K 100, can be deduced from the following formula :

$K_{100} = \frac{1207 \Delta}{R}$, or, by computing R from the specific gravity :

$$K_{100} = \frac{1207 \Delta}{233 (D-1)} = \frac{5.18 \Delta}{D-1}.$$

Prof. Poehl has made over 2000 osmotic tests in analyses for the determination of the other co-efficients of urine. As far as can be gathered from them, the facultative osmotic value for a normal urine is equal to 450.

$$K_{100} = \frac{1207 \Delta}{R} = 450.$$

This osmotic coefficient of urine, as clinical experience shows, has proved very useful for diagnostic, as well as prognostic, purposes. By its use Prof. Poehl¹²³ discovered a new biological law which he communicated in 1899 to the Paris Academy of Sciences.

It appears that in our organism the processes of oxidation are not only a source of energy in the form of heat which is measured by calories, but at the same time they represent a great kinetic energy which takes effect in the shape of osmotic force and is estimated in atmospheric pressure. Prof. Poehl arrived at this conclusion concerning the influence of the oxidation on the osmotic tension in the organism when he observed the influence of *Sperminum-Poehl* on the metabolism. At the same time he satisfied himself¹²⁴ that in all forms of auto-intoxication caused by diminished textural respiration, a lowered osmotic coefficient of urine was observable.

If this decrease of the textural respiration is brought about by the acidulation of the textural juices from over fatigue and over irritation of the nervous and muscular tissue, or from any cause whatever, the other coefficients of urine give evidence thereof. We refer the reader to a series of urinalyses by Prof. Poehl, which he published in an article in the "Wratch" 1899, No. 34, entitled "The osmotic pressure of the juices of the body and its relation to the development and the removal of pathological conditions."

There exists consequently a direct connection between the osmotic pressure of the urine and the osmotic qualities of the

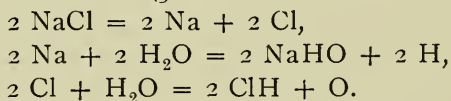
blood and the textural juices, from which the osmotic coefficient of the urine, with normal function of the kidneys, characterises the osmotic conditions of the textural juices.

§ 51. The coefficient of the electric conductivity of urine

As in the dissociation the number of the electrolytes increases, so also at the same time the relative electric conductivity of the solution increases. The absolute electric conductivity depends, of course, on the number of the electrolytes in the solution, and will therefore decrease with the decrease of the concentration. In order to form an idea of the relative conductivity of the dissolved compounds in the urine, Prof. Poehl has suggested a coefficient analogous to that of the osmotic pressure (K_{100}). This is a coefficient which expresses the conductivity in $\frac{\text{Ohm}}{\text{cm}}$ for a cent. per cent. solu-

tion of the compound to be examined. It must be understood that this coefficient furnishes only an approximate idea of the number of electrolytes contained, as the degree of the dissociation present depends on the concentration. We shall mark his coefficient of the electric conductivity with $L=100$, which is arrived at after Kohlrausch's method.

The electric conductivity of the textural juices certainly plays an important part in the organism. The ions which appear in the electrolysis cause *in statu nascendi* a series of important biological-chemical processes. Brasch,¹²⁵ for instance, explains the action of the NaCl in the electrolysis in the organism by the following form :



Of course, these processes do not go on in the organism in quite so simple a manner, still we believe that a similar process accounts for the significance of the NaCl in the textural respiration.

The examination of the electric conductivity of the textural juices, as well as the urine, furnishes an essential addition for the kryoscopic investigations. By the use of the above-mentioned coefficient of Poehl, we gain some insight into the solution of the question as to the extent to which the processes of dissociation participate in the development of the osmotic tension, and to what extent the conductivity is influenced. The therapeutic effects of the bromides, apparently

are to be accounted for by a relative decrease of the conductivity, as is evident from the investigations of Pöchl.

The oxidation, as is to be expected, is in the closest connection with the formation of dissociable compounds, such as electrolytes. This, of course, causes an increase of the electric conductivity of the textural juices. This latter fact is to be explained by an increased "part-pressure" of carbonic acid caused by the oxidation, through combustion of the organic acids. This circumstance, according to the manifold investigations of Hamburger, Zuntz, Loewy, Richter, v. Korányi, and Zikel,¹²⁶ causes the appearance of diffusible bases in the blood, and the exit of NaCl out of the erythrocytes. In this way the alkalinity of the blood is increased, and some electrolytic material passes over into the serum. Thus the opinion which was expressed some time ago by Prof. E. v. Eichwald—namely, that the relative increase of NaCl in the urine in proportion to the urea is an argument for an increased taking up of oxygen, receives a new confirmation. In fact, this coefficient of Eichwald has to the practising physician an enormous value for the prognosis and the judging of the vital energy of the organism.

Clinical observations with simultaneous employment of the above-mentioned coefficients of urine furnish us not only with the possibility of demonstrating that the metabolism of the organism is really disturbed, but they give us at the same time a qualitative, as well as a quantitative, insight for the judgment of this disturbance. The rational urinalysis furnishes us with the means of ascertaining in disturbances of the metabolism, not only the presence of an auto-intoxication, but also its character and stage, as Pöchl has demonstrated by a large series of urinalyses, as well as in written discussion thereupon.

Further, the rational urinalysis is of still greater value to the practising physician, and also to the patient at the same time. It is not only sufficient to form a right diagnosis, but it is also of great value to have an objective method by which an account may be given as to how far the therapy employed answers the desired end. As the coefficients of urine furnish us with an insight into the condition of the metabolism, and as, at the same time, the deviation from the rule is, through

§ 52. Urinalysis not only renders assistance for the diagnosis, but serves also to control the therapy employed

the coefficients of urine, expressed in comparable mathematical values, the coefficients of urine offer the possibility of judging the success or failure respectively, that is, the non-appearance of the desired therapeutic effect. As rational organotherapy can only influence the metabolism and a direct damaging effect is excluded, the practising physician has the possibility of controlling his therapeutic proceeding in chronic diseases by the urinalysis, and at the same time of judging quantitatively to what extent he has influenced the *ens morbi*.

Hitherto the autopsy has been the only certain guide to the diagnosis, but it was unfortunately applicable only after death. The urinalysis, however, furnishes us during the life of the patient with a practicable control, not only for the diagnosis but also for the treatment to be employed.

CHAPTER II

A FEW WORDS AS TO JUDGING THE VALUE AND THE PRACTICABILITY OF THE REMEDIES EMPLOYED IN ORGANOTHERAPY

IT is a remarkable phenomenon in practical medicine that the physician, apart from the use of surgical apparatus, can give himself but little account of the quality of the remedies employed in internal medicine. The surgeon pays to his instruments and his bandages the attention which is indispensable for the completion of his task. He will and must give himself an account of the degree of the antiseptics of his bandages, or of the perfection of their asepsis as well as that of his instruments. He generally goes so far with his sepsis in this direction that he relies only on the material which he himself made aseptic.

§ 53. The
therapeutic
value of
different
organo-
therapeutic
preparations

The internal practitioner cannot give himself an account of the therapeutic means he employs. He can only endeavour, as far as possible, to control their therapeutic effect. As this, however, offers some apparent difficulties, he has often given up entirely the criticism of the remedies employed. In consequence of this uncritical conduct as to the therapeutic means, it is easily seen that he is led only by the great quackery which has been employed for this or that remedy. Considering the infinitely large number of remedies which of late have been introduced into practical medicine, it is almost impossible for the physician to judge personally the value of a new remedy. Only in the light of these unfortunate conditions is it possible to explain how in Organotherapy some remedies come into use which could by no means stand before a searching criticism. We refer here in the first place to a series of organo-preparations which have had their origin in England, Belgium and Germany. These preparations are nothing more than a dried and powdered mass of tissue freed from its fat. Such

preparations have been and are still employed, even in university clinics. Prof. Poehl more than ten years ago called attention to the faults of such preparations.

Prof. Posner¹²⁷ has proposed a very simple method of examining such preparations. He proceeds as follows: The powder of the organo-preparations, stirred up in water, is stained with a triacid-solution. The variety of the textural elements is clear even to the unaided eye. The powdered mass shows also on the filter, by different staining of the particles, the varying characters of the textural elements composing the preparation. Considering that these tissues have been dried in a vacuum under the most favourable circumstances, and that later the anaërobic post-mortem life of tissues, which Armand Gautier described, has appeared, one can imagine how little suitable such preparations are to take the place of the inner secretion of the respective glands, and how rarely they attain to the requirements of Organotherapy.

Prof. Poehl has pointed out on many occasions that the unfortunate experiences endured from preparations of thyrocoidin (their noxious influence on the heart) are to be attributed to the post-mortem products of the thyroid gland. The observations of Prof. Affanassieff, Prof. Prince Tarchanoff, Serapin, Schomacker, etc., have shown that a rationally made preparation of the thyroid gland, such as *Thyroidinum-Poehl*—which is free from toxins and contains only the synergetic group of the active constituents of the thyroid gland—may be therapeutically employed continuously without exercising any detrimental influence on the heart. If satisfactory therapeutic effects in some cases were obtained with dry organs, this is in favour of the assertion of Prof. Prince Tarchanoff, namely, that some constituents of our tissues have great power of resistance. Still, the conclusion should not be drawn therefrom that dried and powdered glands might be considered as rational preparations.

In the discussion of organotherapeutic remedies we shall consider only those which reach the standard of the requirements of the present day. We shall not, however, give any word of warning against specific preparations or speak derogatively of their manufacturers.

If it requires a great deal of circumspection and precaution to select the proper organotherapeutic remedies for interna

use, still more circumspection is necessary when the hypodermic application of organotherapeutic remedies is made. In this field the lack of criticism is strikingly apparent.

Soon after Brown-Séquard and his school employed the testicle-extracts, some doubts were expressed about them. Strange to say, however, they all tended in one direction, namely, the possible presence of pathogenic micro-organisms. Chamberland first suggested for this purpose the filtration through kaolin filters with or without pressure of carbonic acid; and with this most authors were satisfied. Prof. Poehl in 1891 had pointed out that such a filtrate may be free from micro-organisms, but the toxins and the enzymes must be contained in it unchanged.

§ 54. Organo-preparations and their hypodermic use

Experience teaches us also that such extracts produce some very noxious by-effects, while in the injections made by the thousands with the isolated constituents or synergetic groups (such as Prof. Poehl introduced) there were never any bad effects observed nor any local irritation from the hypodermic injection. These preparations contain only the normal physiological constituents. Therefore they must be harmless.

Finally, from the suggestion of Prof. Poehl still a third use of organo-preparations may be mentioned. It is that of preparations soluble in water together with normal salt solution (Poehl) which, in consequence of their extraordinary diffusibility, may be used as enemata intended to be retained. Experience shows that they have an effect similar to that of hypodermic injections. Of course, these preparations must also be free from toxins. It must be taken into consideration that, when introduced as enema, the soluble constituents come directly into the circulation, and that even the protection which the liver affords to the organism after introduction of the substances *per os*, is in this case partly omitted. Therefore, in the employment of organotherapeutic remedies *per clysmata* one must proceed in their selection with just as much circumspection as precaution.

§ 55. Organo-preparations used as enemata

CHAPTER III

SPERMIN—SPERMINUM-POEHL

§ 56. Chemistry of semen and of the crystals of spermin

THE chemistry of animal semen has been a very difficult problem since the beginning of the last century, and the literature on the subject is very large.

The characteristic constituent of the sperma, *Spermin*, was observed as far back as 1865 by A. Böttcher.¹²⁸ He found that in human semen, when drying up slowly, some microscopical crystals—some long-drawn octaëders—are formed. He, however, could not determine the chemical nature of this compound. He published his observation under the title, “Colourless crystals of a body resembling albumen, prepared from human sperma.” Schreiner,¹²⁹ in 1878, succeeded in isolating the base of these crystals, *Spermin*; but, as we shall see later, not in a perfectly pure condition. Anyhow, Schreiner deserves credit for having been the first to recognise some of the characteristic chemical qualities of *Spermin*. The elementary analysis, however, which Schreiner made, led him to the wrong formula, C_2H_5N .

Ladenburg and Abel,¹³⁰ relying on the analytic data of Schreiner, expressed the opinion that in all probability *Spermin* was identical with æthylenimin (C_2H_4HH). A year later (1888) Kobert,¹³¹ evidently through a misunderstanding, recognised *Spermin* as identical with æthylenimin, and even gave to the polymeric diæthylenimin (piperazin) the name “dispermin.”

§ 57. The chemical formula of spermin

When Prof. Poehl,¹³² in 1890, commenced his investigations on *Spermin*, he had, on account of the assumption prevailing in published works, to clear away the unfounded identity of *Spermin* with æthylenimin. This assumption, which later on¹³³ he refuted by means of the following analytic data, gave occasion for a number of misunderstandings and to a controversy.*

* In consequence of this, as it appeared later, unfounded identifica-

This controversy was ended by the eminent Russian chemist, Prof. Mendelejeff,¹³⁵ who exposed the erroneousness of the criticisms, which were not even unprejudiced, of Trapp, Aurep, Frenkel, and Herzenstein.

Proof that the assumption of the identity of *Spermin* with æthylenimin and with piperazin is unfounded, has been furnished by Prof. Poehl from the following results of the elementary analysis of the platinum-double-salt made from pure muriate of *Spermin*.

Carbon	11.89	per cent.
Hydrogen	3.36	"
Nitrogen	5.89	"
Platinum	38.21	"

The analysis of a platinum-double-salt, which he made from the phosphate of sperminum dissolved in muriatic acid, gave a content of 38 per cent. of platinum.

These numbers correspond to a platinum-salt with the

tion of *Spermin* with Æthylenimin, by the factory of Schering in Berlin, under the name of "*Spermin*"—piperazin was offered in trade and a privilege for ten years was granted to the Berlin Chemical Factory in Russia for the manufacture of this preparation, which was improperly named "*Spermin*" (C.—Петербургск. Ведомости. October 17, 1890). In comparing the preparation of Prof. Poehl with that of Schering, of course, some chemical differences were found. From this, several not quite unprejudiced critics of Poehl's *Spermin*-preparation (Trenkel, Prof. Aurep, Prof. S. M. Wassiljeff, Herzenstein, Prof. Trapp, and others) were induced to institute a not always proper polemic. They did this partly openly, partly anonymously. To characterise the position the following words from an open letter of Prof. Mendelejeff to Prof. Poehl may be quoted ([Wratch, in Russian], 1890, p. 1106, and "St. Petersburg Med. Wochenschrift," 1890, p. 437): "Interference from retrogrades and laymen must not deter those who have directed their endeavour to the investigation of the truth.—The incident caused by your *Spermin* is very instructive for the history of the medical preparations and your preparation, to judge from what I heard from several—not beguiled—sides, promises to take a respectable place in the row of those new remedies the investigation of which belongs to the questions of the day. Your *Spermin* is also the real *Spermin*, and that preparation which was placed before you as sample, is not at all *Spermin*, but the long known diæthylendiamin, piperazin. And now proceed, with the Lord's aid, without worrying over the attacks being made on you and your *Spermin*. The truth will conquer." These words of Mendelejeff, the Nestor of chemistry, have been fully corroborated. From a scientific point of view the non-identity of *Spermin* and piperazin was settled. In medical and pharmaceutical practice, however, the confusion continues, and even to the present time piperazin is often used for sick persons in place of *Spermin*.

formula $C_5H_{14}N_2 \cdot 2HCl$, $PtCl_4$, which requires the following values :

Computed.	Found by Poehl.	Computed after Schreiner's ¹³⁰ Formula.
C_5 . 60 . 11.73 per cent.	11.89 per cent.	9.6 per cent.
H_{10} . 16 . 3.13 ..	3.36 ..	2.42 ..
N_2 . 28 . 5.47 ..	5.89 ..	5.65 ..
Cl_6 . 213 . 41.63 ..	—	42.98 ..
Pt . 194.6 . 38.04 ..	38.21 ..	39.26 ..
511.6 100.00 ..	—	100.00 ..

The gold-salt of Spermin, in two determinations, furnished 50.51 per cent. of gold. The formula $C_5H_{14}N_2 \cdot 2HCl \cdot 2ClInCl_3$ calls for 50.31 per cent. of gold. According to the formula of Schreiner, 50.31 per cent. of gold are required.

The organic base which is at the bottom of these double-salts would have the composition, $C_5H_{14}N_2$.

The analytic values which Prof. Poehl found may correspond to a whole series of compounds of the following general formula— $C_{10}H_{26}N_4 \cdot n(C_5H_{12}N_2)$.

The composition per cent. of these different bodies shows, as we see, slight variations. The above-mentioned elementary analyses were made by Prof. Poehl in 1890. Afterwards he several times analysed the gold-salt and the chloroplatinate, and found always, with great uniformity, values which indicate the empiric formula,¹³⁷ $C_5H_{14}N_2$.

§ 58. Difference between spermin and piperazine

It has been established by his investigation that Spermin is in no way identical with æthylenimin or diæthylendiamin (piperazin), as the proportion of the atoms of carbon to those of nitrogen is in diæthylendiamin as 4 : 2, and in Spermin as 5 : 2, and that of the atoms of hydrogen to those of nitrogen is in diæthylendiamin as 10 : 2, while in *Spermin* it is 14 : 2. Further the identification of piperazin with “dispermin,” which Kobert so improperly suggested, should be dropped.

After Schering's factory, misled by Kobert's statements, had given the first occasion for the confusion of *Spermin* with piperazin, the mistake was recognised and admitted by the factory in consequence of the letter of Prof. Mendelejeff. The difference between diæthylendiamin (piperazin) and

Spermin was also established about the same time by J. Sieber.¹³⁸ Finally, also, W. Majert and Albert Schmidt¹³⁹ recognised the difference between *Spermin* and piperazin, and demonstrated it by means of iodine-bismuth-compounds. Those of *Spermin* form orange-coloured, flaky or feather-like arranged, microscopical, pointed little needles; those of piperazin deep garnet-red, rectangularly stretched, microscopical little plates.

The difference between *Spermin* and piperazin was also recognised by A. W. v. Hofmann.¹⁴⁰ And Prof. C. Edwald, in his "Handbook of General and Special Pharmacology," expressed himself energetically against the identity with piperazin, and this, on the ground of his own experience, which he had obtained (together with Dr. Dronke) in the manufacture of *Sperminum hydrochloricum*.

Prof. Poehl obtained different results from the elementary analysis than those of Schreiner, probably because he removed the albuminous bodies as completely as possible, and recrystallised the phosphate several times, before using in his analysis the base, or its salts, which the test required.

For the wholesale manufacture of *Spermin* Prof. Poehl found the testicles of bulls and stallions most suitable. He subjects these to a very exact comminution, in presence of water, making a fine emulsion, and extracts them with acidulated water. Then the albuminous bodies are separated from the fluid. Very much depends on the perfect separation of the albuminous bodies, as a remainder of albuminous bodies seriously interferes with the crystallisation of *Spermin* as phosphate of *Spermin*. Prof. Poehl has employed very varying methods for the removal of the albuminous bodies, and he always obtained the pure phosphate of *Spermin* simultaneously with the entire removal of the albumen. It is of great importance that during the process the solution should be protected against fermentations and the influence of bacteria. Poehl¹⁴¹ always observed the methods of employing asepsis and antiseptics in the manufacture of *Spermin*, as he recommended in 1886 and 1887. It is apparent that in the manufacture of physiological preparations that decomposition should be prevented. And it is still necessary to call attention to this point, because on several occasions, even after the publication of

§ 59. Manufacture of spermin

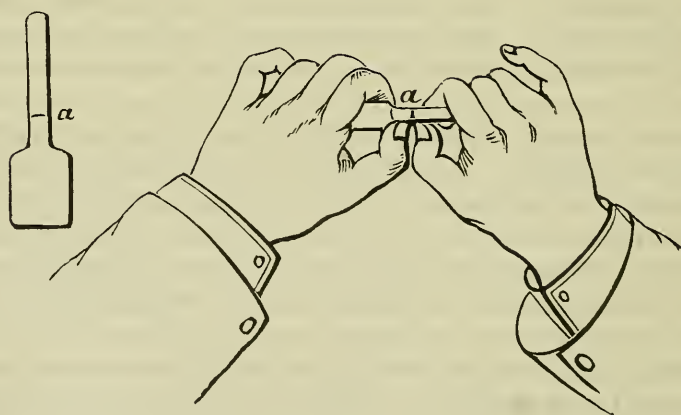
the articles of Schreiner and Poehl, the assertion has been made, though by very incompetent persons only, that Spermin did not exist and could consequently not be gained from the testicles of animals. (A. Jürgens, E. Johanson, Majert, Schmidt,¹⁴² etc.) For the precipitation of *Spermin* the phospho-tungstic acid or the phosphomolybdenic acid serve best. In careful separation with baryt the base becomes free. The prominent quality of *Spermin*, namely, that of forming with phosphoric acid some well crystallised salts, is used for the manufacture in a pure condition. Prof. Poehl, however, either decomposed this comparatively pure phosphate carefully with baryt, washed the base with ether, and transferred it again into the phosphate, or he recrystallised the phosphate of Spermin several times out of hot water.

Spermin is a fairly strong base, and readily forms some well crystallised salts which are hygroscopic, and, therefore, little durable in the air.

For medical purposes Prof. Poehl proposed the muriate $C_5H_{14}N_2.HCl$ in the following forms :

§ 60. Sper-
minum-Poehl
pro injectione

The **Sperminum-Poehl pro injectione subcutanea in ampullis** for hypodermic injections is a sterilised two-per-cent. solution of the muriate of Spermin in physiological solution.



The **Sperminum-Poehl pro injectione** is furnished in glass ampullæ closed by smelting, each of which contains the quantity (ca 2 ccm.) necessary to fill a Pravaz syringe.

The filling of the Pravaz syringe is best made in the following way: 1. Needle and syringe are disinfected with boiling water, and the piston is examined for tight fitting. 2. By swinging the ampulla with quick, energetic motions of the hand the fluid is driven back from the neck of the ampulla into the basin. Then the neck is broken in the place marked with a line. To avoid injury to the fingers the ampulla should be wrapped into a clean towel. 3. The needle is removed from the syringe, and the open end of the latter is introduced into the ampulla, which is inverted. 4. With slow, equal traction of the piston the contents of the ampulla are received into the syringe, to which, 5, at the end of this procedure the disinfected needle is attached.

Finally a few drops are driven out of the syringe, which is turned upwards, to expel all air present, and the needle is introduced under the skin or into the muscle.

Hypodermic injections are best made in one of the extremities or around the shoulder-plates; still easier is it to make them into the muscles of the regio glutæa.

Repeated injections in the course of a day are rarely necessary. In most cases the injections are made only once in a day. Even this is necessary only in the beginning of the treatment up to the tenth or twelfth injection. Later on they are made at greater intervals.

After it became evident that Spermin has also a curative effect when taken internally, a four-per-cent. alcoholic solution of Sperminchloridchloronatrium is made in the laboratory of Prof. Poehl & Sons under the name of **Essentia Spermini-Poehl**. By means of the addition of a little glycerine it keeps unchanged for a lengthy period. To cover the disagreeable smell of spermin the solution is flavoured.

§ 61. **Essentia
Spermini-
Poehl**

The free base has a pronounced smell of spermin, while, as Poehl satisfied himself, neither of the salts of spermin has such a smell. The acid salts are perfectly free from smell, while the neutral ones have a slight smell of honey, which, on the addition of alkali, passes over into a more or less distinct smell of sperma. With the characteristic reaction of the smell of spermin and its salts we shall deal later.

The **Essentia Spermini-Poehl** is furnished in bottles and is dispensed in doses of from twenty to thirty drops in alkaline mineral waters (Vichy, Ems, Bilin, Borshom, etc.) to be taken in the morning on an empty stomach, as well as in the course of the day.

The internal use of the essence of spermin has the same stimulating effect as the hypodermic injections, with the

difference, however, that in the former the curative effect appears slower than in the latter.

§ 62. Sper-
minum-Poehl
siccum pro
clysmate

Quite recently in the laboratory of Prof. Poehl & Sons a preparation of spermin has been made in a dry state which is intended for employment as a clysmata to be retained. This **Sperminum-Poehl sicc. pro clysm.** contains one part of *Sperminum-Poehl* to four parts of physiological *Sal physiologicum-Poehl*.

Sperminum-Poehl sicc. pro clysm.

The hypodermic injections are not always (as, for instance, in grave forms of diabetes) nor everywhere possible. Besides, it has been shown that spermin is also readily absorbed from the bowels, and the same results are obtained in this way as by the hypodermic injections. For this reason the chemical laboratory of Prof. Poehl & Sons manufactures a **Sperminum-Poehl sicc. pro clysm.**

This preparation is furnished in tubes of 1.0 gm.

Every tube contains 0.2 gm. *Sperminum-Poehl*, and 0.8 gm. *Sal physiologicum-Poehl*.

To use this preparation the contents of a tube (1.0) are dissolved in half a tumblerful (100 ccm.) of hot water and are introduced warm (at blood-temperature), with a rubber-bag or a syringe with a rubber tube (as in the case of nutritive enemata), high up into the rectum. If injected slowly and warm into the rectum, the solution does not irritate the bowel, is well retained and readily absorbed.

Repeated experiments have demonstrated that the effect of such Spermin-enemata is the same as that obtained by the hypodermic injections of *Sperminum-Poehl*.

The above-mentioned solution of spermin is isotonic with the textural juices, and therefore does not cause the least irritation of the mucous membrane of the bowels. The absorption takes place quickly. Thanks to the important osmotic qualities of the *Sal physiologicum-Poehl*, this mixture operates by an increase of the osmotic tension of the juices of the body, by which the work of the heart and kidneys is lessened. The kidneys, according to *Hamburger* and *v. Koranyi*, play the part of a real lymphatic heart in a normal condition of the osmotic tension in the organism. *Sperminum-Poehl sicc. pro clysm.* brings the decreased osmotic tension of the textural juices back to the normal—firstly, because the *Sal*

physiologicum-Poehl on its own account increases the osmotic pressure, and, secondly, because *Sperminum-Poehl* removes that which injures the energy of the processes of oxidation, and thereby the osmotic pressure. Here it should be noticed that the *Sal physiologicum-Poehl* not only contains NaCl, but all the osmotically active constituents of the blood serum.

From these statements, it will readily be seen that **Sperminum-Poehl sicc. pro clysm.** is not only capable of supplanting the hypodermic injections, but also of frequently producing stronger effects in different auto-intoxications, as, *e.g.*, in different forms of anæmia and inanition, in arterial sclerosis, and in different diseases of the nervous system (neurasthenia, tabes). The therapeutic value of *Sal physiologicum-Poehl* in acute diseases such as typhoid fever, dysentery, etc., has been demonstrated by Dr. Ljubomudroff.

According to the observations of Prof. Poehl, the influence of **Sperminum-Poehl sicc. pro clysm.** on the metabolism and the processes of oxidation in the organism is just as quick and energetic as the action of the hypodermic injections of *Sperminum-Poehl*. In proof of this, in a case of anæmia and neurasthenia after four enemata in the course of six days the coefficient of the energy of oxidation, Robin-Poehl, was increased from **86.71** to **90.84**. The coefficient of Zuelzer, which indicates the intensity of the metabolism in the nervous tissue, rose from **18.6** to **20.2**, that is, the previously existing accumulation of products of metabolism gave way to a normal excretion, and at the same time the hyaline cylinders disappeared from the urine. The osmotic coefficient of urine (Poehl-Bouchard) was below the average, and rose nearly to the normal after four enemata. The coefficient of the alkalinity of the blood (Poehl-Leyden) rose from **35.6** to **67.2**. From these data it is clear that in this case there was a combustion of the organic acids of the textural juices which had previously lowered their oxidation. In this way, under the influence of **Sperminum-Poehl sicc. pro clysm.** the main cause of the auto-intoxication disappeared.

Not only does this new preparation in many cases replace the hypodermic injections, but it has also some advantages over **Sperminum-Poehl pro injectione**. This is so in arteriosclerosis and infectious diseases. In cases of œdema,

however, when a further increase of the osmotic pressure is undesirable, only hypodermic injections of **Sperminum-Poehl pro injectione** will be useful.

Thus the physician has now at hand three preparations, namely

Essentia Spermini-Poehl,

Sperminum-Poehl pro injectione, and

Sperminum-Poehl sicc. pro clysm. which, if properly employed, will provide him with the means of increasing the textural respiration, of bringing the osmotic tension to the normal, and, in this way, of removing the cause of the different auto-intoxications.

We will not trouble with abstruse chemical explanations the reader who takes interest only in the medical and biological aspects of the question, but will touch only those points of the chemistry of spermin which are necessary for the proper understanding of its therapeutic action.

The most characteristic reaction on Spermin is the smell after fresh human sperma, which develops when chloride of gold and metallic powdered magnesium are added to a solution of Spermin.

§ 63. Schreiner's spermin-reaction (smell-reaction)

The smell-reaction appears not only on the addition of chloride of gold to a solution of Spermin in presence of magnesium, as Schreiner thought, but also upon the addition of chloride of any other metal, provided the formation of hydrogen takes place at the same time. Therefore Prof. Poehl uses a five-per-cent. solution of chloride of copper to produce the reaction. As, however, only the free base shows the sperma-smell, care must be taken that no surplus acid is present when the reaction is made. As we shall see later when talking of the katalytically oxidising action of the *Spermin*, under the conditions of reaction already mentioned, oxide of manganese is formed which causes the base to become free. Owing to the generation of hydrogen the sperma-smell is very easily perceptible. It is in any case better to take a great surplus of powdered magnesium,* so

* Schreiner, in a letter to Prof. Poehl, recognises this reaction as absolutely characteristic. Combating this view several opponents of *Spermin* claim that the by-products also give this smell-reaction. However, they fail to state in what manner these by-products are isolated, and what qualities belong to them.

Judgment on such a claim is passed by Dr. Herm. Hager¹⁴⁴ to whom

that in the formation of oxide of magnesium (which, as well as the appearance of the smell, is also an important factor in the reaction) a pap-like mass is formed. This reaction is certainly very easy to execute and extremely characteristic.*

The sensitiveness of the reaction appears from the following fact. If one ampulla of *Sperminum-Poehl* pro injectione, which contains a little more than 1 ccm. of a two-per-cent. solution of chloride of spermin, is diluted with water to 500 ccm. (about 0.004 per cent.), a few drops of this solution give the smell-reaction distinctly if the experiment be carefully made.

Although, as before stated, *Spermin* very readily forms a crystallised phosphate, the assumption that in the presence of phosphates it is always precipitated in the form of characteristic crystals is utterly unfounded. For, first, in the presence of small quantities of surplus acid or alkaline, the phosphate of *Spermin* is very readily solvent; secondly, the phosphate is in the presence of several organic compounds easily soluble; and thirdly, an amorphous phosphate of *Spermin* also originates very readily.

Therefore, it is not all justifiable to infer the absence of *Spermin* from the non-appearance of crystals of phosphate of *Spermin*. The conditions under which crystals of phosphate of *Spermin* are obtained from a particular solution are sometimes very hard to establish.

For the phosphate of *Spermin*, as such, the form of the crystals of Böttcher-Charcot-Leyden is highly characteristic, and Prof. Van Ermengem very properly compares it with that of the *Diatomea Pleurosigma*. It is very difficult to obtain these curved crystals artificially. In proof of this Schreiner's words¹⁴⁷ may be quoted: "The *f*-shaped formation of the arch-surfaced combination of prismatic and pyramidal

§ 64. Crystals
of phosphate
of spermin

the Science owes so many corrections in both medical and pharmaceutical chemistry. He says:

"Schreiner expressly admits as characteristic the reaction with chloride of magnesium and gold in which the smell of fresh sperma appears. Poehl also pronounces this reaction as characteristic, and as conclusive evidence of the presence of *Spermin*. Messrs. Trapp, etc., admit that Poehl's preparations give this reaction, but they attach no importance to this, because, according to their statement, the by-products from the manufacture of *Spermin* give the same reaction. As the chemistry of animal semen has very many interesting features, it would be very desirable if these gentlemen would, at the earliest opportunity, communicate to the world their knowledge concerning the bodies which accompany *Spermin*. We should then be probably enabled to control more exactly the statements made by the opponents just mentioned. To turn to another aspect of the question, it will suffice to mention that the experts in the well-known factory of Merck in Darmstadt, have declared¹⁴⁵ that their experiments for the purpose of obtaining *Spermin* gave a negative result; while Messrs. Majert and Schmidt, who are employed in the scientific laboratory of Schering's factory, have stated that their attempts to obtain *Spermin* from the testicles of animals had been unsuccessful.

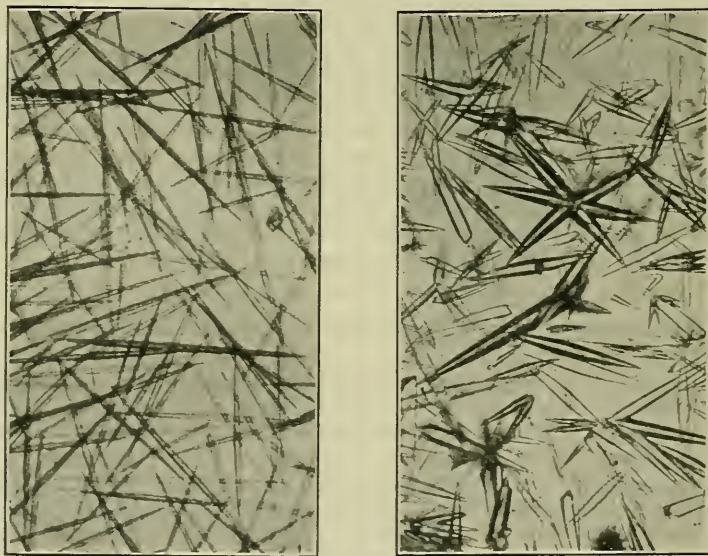
* For the reaction Poehl uses powdered magnesium as employed for illumination in photography. Should the magnesium contain grease (as often is the case) it should be removed by means of ether or benzine.

shapes, which Böttcher draws, I have also observed very carefully. I have, however, never seen it in recrystallised material. I have seen it in dried up Sperma only."

Prof. Poehl, by recrystallising the phosphate of Spermin out of warm solutions, often obtained these *f*-shaped, curved, and convexed crystals. The accompanying photograms represent such crystals of phosphate of Spermin. As in the case of sperma, double crystals may often be seen.

As the crystals of the phosphate of Spermin dissolve in a weak acid, as well as a slightly alkaline medium, the careful control of the amphoteric reaction of the medium is of the utmost importance; though of itself it is not by any means sufficient wherewith to obtain the crystals.

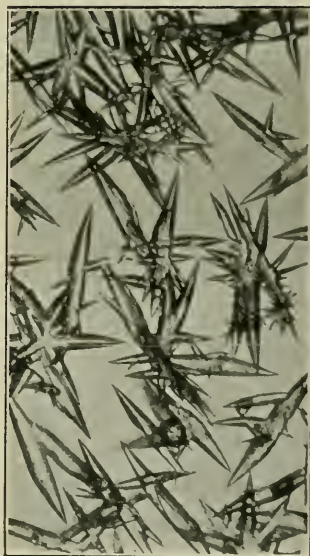
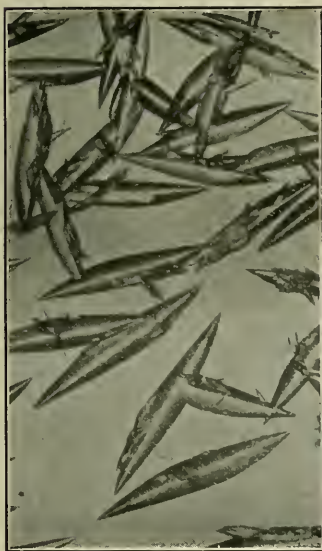
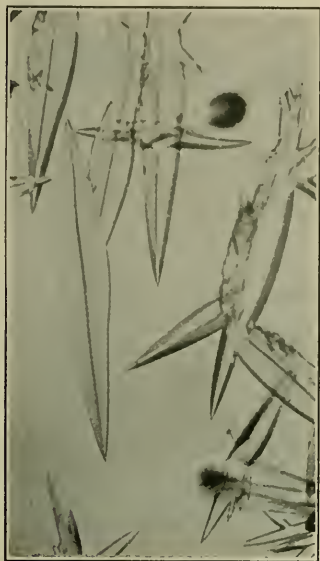
Under an exact observation of certain conditions, however, the crystals can be always obtained, and as they present many interesting features, Prof. Poehl gives very simple instructions as to how the characteristic crystals of phosphate of Spermin may be obtained very readily out of every ampulla of *Sperminum-Poehl* intended for hypodermic injection.



Crystals of Phosphate of Spermin.

A cubic centimetre of the solution of *Sperminum-Poehl* in the ampullæ is acidulated with phosphoric acid (4 drops of a solution of 1 part of phosphoric acid, sp. gr. 1.13. to 9 parts of water) and carefully neutralised to the amphoteric reaction (with about 4 drops of a solution of 1 part of caustic soda to 70 parts of water). After adding 3 ccm. of 95° alcohol the formation of the crystals of phosphate of Spermin occurs within a few (say 1 to 10) minutes. The mixture is made in a large watchglass which can be placed under the microscope. If correctly made, a cloudiness appears in the mixture, but disappears almost immediately. Then stir it with a glass-rod, to promote the crystallisation, when with a small diaphragm, of weak

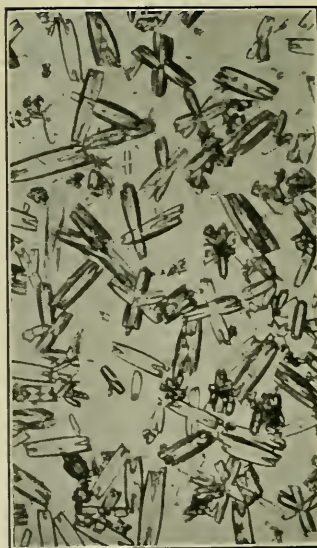
power and long focus, the formation of the crystals can be seen in the different strata of the fluid. The concentration of the phosphoric acid as well as of



Crystals of Phosphate of Spermin.

the alcohol must be carefully observed in order to obtain some well-developed acute-angled crystals. Otherwise we first obtain an amorphous phosphate,

which assumes the crystallised shape but slowly, and occasionally fails altogether.



Crystals of Phosphate of Spermin.

These crystals, being optically active, present a pretty effect when observed in polarised light.

When thus crystallised in the presence of alcohol the forms obtained are chiefly sharp-pointed or rectangular in shape. Later, however, by re-crystallisation from a hot watery solution under slow cooling, other forms are obtained. Seeing that Prof. Fürbringer denied the identity of these varying forms, Prof. Poehl made an extensive series of crystallisation experiments, and photographed the shapes of the crystals he obtained. In a collection of over three hundred photographic pictures he has furnished the proof that phosphate of Spermin crystallises in all the transitive shapes—from the acute to the obtuse-angular ones, from the straight to the arch-surfaced and the curved forms. Poehl has also noted the formation of double-crystals, as they often appear in sperma. The photographs here reproduced illustrate the process.

Besides, Prof. Poehl mentions that he also compared the smelting-points of these crystals, and states that he could discover no difference between them. Their smelting-point is between 130° and 135° C. Phosphate of Spermin very readily loses the water of crystallisation even at ordinary temperature in the exsiccator over sulphuric acid. Naturally, the loss of water involves an essential change in the smelting-point.

The assertion that the gold-double-salt of Spermin has a characteristic shape, according to Poehl, is not well founded, for the simple reason that according to the conditions of crystallisation, the gold-salt is precipitated in different shapes and the gold-salt of Spermin resembles several other gold-salts.

One reaction on *Spermin* has yet to be mentioned which has lately been much discussed in various journals.

§ 65. Florence-reaction

Prof. Posner¹⁴⁸ was the first to point out that the solution of Kalium-trijodür (1.65 gr. Iodine and 2.54 gr. Iodide of Potassium to 30 gr. water—the solution being made with refrigerations), which Prof. Florence¹⁴⁹ recommends for the detection of sperma, is a good reagent for Spermin. Prof. Posner first described the appearance of the characteristic crystals on treatment by *Sperminum-Poehl* (the solution from the ampullæ for hypodermic injection) with this reagent. Florence was of the opinion that the solution of Kalium-trijodür gave some crystals of the shape of the Hæmin-crystals of Teichmann, only in the case of human sperma he stated that he recognised from this reaction a special kind of Spermin, viz., “Virisperm in.” Such a reaction would have been of the greatest value for forensic-medical purposes. Prof. Posner, however, has shown that Florence was mistaken in this conclusion. Further, Prof. Poehl always obtained the characteristic crystals of Tri-jod-spermin from animal sperma¹⁵⁰ when the reaction was made in a particular manner. Like all reactions with crystallisation, this must be carefully executed. He notes that with *Sperminum-Poehl* this reaction succeeds so easily and so certainly that it may be considered as constituting an exception to the rule. It is therefore very surprising that Florence did not succeed in obtaining the reaction with *Sperminum-Poehl*. It would almost appear that he had used an adulteration of *Sperminum-Poehl*. It is matter for regret that adulterations of this remedy are so frequently met with everywhere.

The solution of Kalium-trijodür must be made exactly after the directions of Florence. After having been kept in the cold for at least twenty-four hours, it is in good condition and ready for use. One drop of *Sperminum-Poehl* out of an ampulla is brought on an objective-glass and a thin thread of cotton is so placed into the drop that its free end stands out from under the cover-glass. With a glass-rod a drop of the solution of

Kalium-trijodür is brought into contact with the free end of the thread and the brown solution of Iodine streams along the thread to the solution of Spermin. A brown-red cloudiness is at once formed and within a short time (from 1 to 5 minutes) the crystals, exactly similar in form to Teichmann's Hæmin-crystals, can be seen with the microscope, shooting out in large quantities. The crystals grow visibly till finally the whole field of vision is covered with them. Occasionally after a short time they disappear. If, then, more of the Kalium-trijodür solution be brought to the solution of Spermin through the thread, the crystallisation recommences. This reaction of Florence's has been described by Wyatt, Johnston¹⁵¹ and W. F. Whitney¹⁵², as well as by Max Richter¹⁵³ (in the Institute for Forensic Medicine of Prof. v. Hofmann in Vienna). From the investigations of the last-named it appears that this reaction is not specific for Spermin, as lecithin, cholin, and muscarin also give similar typical crystals.

Hence, the formation of crystallised iodine-compounds is not characteristic of Spermin exclusively, but for a whole series of products of retrogressive metamorphosis of albuminous bodies, as well as for cholin. N. Bocarius¹⁵⁴ claims that in the semen it is not the Spermin, but the cholin which gives the reaction of Florence. It is, however, evident that during all his investigations he has not had any Spermin whatever. Briefly, he has repeated the mistake of Wajert and Schmidt, already referred to.

The spermin-salt of IH is just as readily soluble as that of ClH and BrH.

According to the experiments of Poehl, the substitution-products of Spermin with iodine, as well as with bromine, are not readily soluble. It appears, therefore, that bromine also gives a compound analogous to that yielded by Spermin, and as little soluble (Tribromspermin ?)

CHAPTER IV

ON THE DISTRIBUTION OF SPERMIN IN THE ORGANISM AND THE ACTION OF SPERMINUM-POEHL ON THE METABOLISM

PROF. P. FÜRBRINGER,¹⁵⁵ in 1881, set himself the task of solving the question which constituent of the seminal plasma furnishes the crystals of the sperma. In the ejaculated sperma, liquid as well as dried up, they are found regularly. For this reason Fürbringer examined the contents of the seminal vesicles of 43 corpses, as well as the juice of the prostatic gland, for the presence of the crystals. He found that spermatic crystals crystallised from the prostatic juice of the corpse in 90 per cent. of the cases (during the evaporation on the objective-glass), while the contents of the seminal vesicles furnished them only in 15 per cent., and even then in extremely small quantities.

§ 66. Spermin
in the seminal
plasma

With the secretion of the prostatic gland of living persons it was different. Fürbringer tried to obtain the secretion by local pressure from the rectum, and he succeeded, especially when the bladder was filled, in getting from twenty individuals quantities varying from a few drops to one ccm., while in other cases, in spite of pressure, the urethra remained dry. It was singular, however, that in the secretion of living persons the examination brought to light no crystals, or a minimum only, compared with the quantity obtained from one drop of the juice from the corpse. Fürbringer looked for the cause of this in a lack of phosphoric acid. The most essential cause in this case is, according to the opinion of Prof. Poehl, the weakly alkaline reaction of the prostatic juice in living persons, while in the corpse the alkaline reaction disappears. When Fürbringer added a little phosphate of ammonia to the prostatic secretion, it was changed within a few hours to a milk-like mass full of large spermatic crystals. Fürbringer fails to state which of the three phosphates of ammonia he

employed. Probably the acid, or perhaps the amphoterically reacting. The weakly alkaline reaction of the prostatic secretion (even of that taken from living subjects) outside the organism passes over into the amphoteric reaction (decomposition of lecithin), and by this means, according to Poehl, the factors for the formation of the crystals are given.

Fürbringer performed a similar experiment with the contents of the seminal vesicles and the secretion of the testicles, again under application of phosphate of ammonia. He did this on ten corpses and found that the crystals appeared in the testicular secretion only occasionally, and in the secretion of the seminal vesicles not at all. He therefore concluded that Spermin does not occur at all in the secretion of the seminal vesicles, while in the prostatic juice it is constantly contained in large quantities. These negative results in the secretion of seminal vesicles and the testicles are probably to be explained by the fact that in the corpse these organs retain their alkalinity longer than the prostatic gland. It is to be noted that the chemical character of the phosphate of ammonia employed in these experiments is not stated. On this occasion Fürbringer also made some observations concerning the sperma-smell, from which he concluded that the prostatic juice obtained by rectal palpitation from the living man showed the most pronounced sperma-smell, while owing to the presence of feculent and putrid by-smells it is rarely present in the juice taken from the corpse.

As already stated, the free base and the basic salts of Spermin have the sperma-smell, while an acid solution of Spermin is free from smell. Prof. Poehl accounts for the fact that Prof. Fürbringer did not observe the smell of sperma in the juice of the prostatic gland of corpses because of the probable spread of the general acidulation of the tissues to that gland.

§ 67. Distribution of spermin in the male and female organism

The foregoing statements by Fürbringer caused the statement to be made that *Spermin* existed only in the prostatic gland. And when Majert, Schmidt, and Lassar-Cohn published their investigations, according to which they could find no *Spermin* at all in the testicles, this opinion received further corroboration. Finally it was generally accepted that *Spermin* occurs only in the prostatic gland, and is a constituent of the male organism exclusively.

This condition of affairs caused Prof. Poehl¹⁵⁶ to institute a series of investigations for the purpose of determining the distribution of *Spermin* in the organism. Therefore he examined different organs of the body in order to ascertain the amount of *Spermin* they contained.

In default of a method of quantitative determination for *Spermin* he had to confine himself to judging the amount of

it in different organs from what he could gain from them by a carefully uniform treatment.

For these investigations, of course, large numbers of different organs, which he received fresh from the slaughter-house, had to be examined. By these investigations, which were made with fresh organs from bulls and cows, he succeeded in establishing the fact that *Spermin* is not, as was formerly believed, a specific constituent of the male sexual organs only, but is also a normal constituent of the female organism. Poehl found *Spermin* not only in the prostatic gland and the testicles, but also in the ovaries, the thyroid gland, the pancreas, the liver, the spleen, etc., and finally also in the blood. Comparing the different results obtained, the testicles contain the largest amount of *Spermin*; then follows the prostatic gland, and after it come the ovaries, the pancreas, the thyroid glands, and the thymus.

Subsequently Poehl satisfied himself that *Spermin* is also produced during the leucolysis. This accounts for the fact that the laudable pus, the "*Pus bonum et laudabile*," has so pronounced a smell of sperma. Here it should be stated that in laudable pus Poehl could always demonstrate an alkaline reaction. In consequence of the alkaline reaction the sperma-smell of the laudable pus is very pronounced, as probably every surgeon has occasion to observe when changing bandages. The "*Pus malignum*" has mostly an amphoteric or an acid reaction.

§ 68. *Spermin*
in laudable
pus

Poehl has also directly demonstrated the presence of *Spermin* in the "*pus bonum*." No great quantity is needed for this, as the amount of *Spermin* is nearly as high as that in the sperma.

This wide distribution of *Spermin* in the organism and its presence in the blood accounts also for the fact that crystals, which later proved to be phosphate of *Spermin*, were long ago found and described so frequently. From the following we shall see that in acidulation of the tissues during life or after death, under certain circumstances *Spermin* is precipitated in the organism as phosphate of *Spermin*. At present we will confine ourselves to hinting at certain significant facts.

§ 69. Charcot-
Leyden's
crystals of
phosphate of
spermin

The first description of these crystals was furnished by Charcot and Robin¹⁵⁷ as far back as 1853. Their attention had been called to these peculiar crystals in the spleen in a case of leuchæmia.

In 1854 Foerster¹⁵⁸ observed the same crystals in sputum, established their insolubility in ether, and gave it as his opinion that they consisted of an organic substance related to phlegm. Harting¹⁵⁹ in 1859 also noticed these crystals in the sputum in a case of bronchitis. He found them insoluble in water, alcohol, and ether; soluble in acetic acid, muriatic acid, and nitric acid; and characterised them as consisting of phosphate of lime. In 1860 the crystals were found by Charcot and Vulpian¹⁶⁰ in leucæmic blood from different parts of a female corpse. In this case the crystals were not noticed on the day of the post-mortem; on following days, however, they appeared with more and more frequency. According to Charcot and Vulpian¹⁶¹ they are brittle, and are insoluble in cold water, alcohol, ether, chloroform, glycerine, and tincture of iodine. In warm water, however, in acetic acid, tartaric acid, lactic acid, sulphuric acid, and muriatic acid, as well as in solutions of caustic potash, soda, and ammonia, they are readily soluble.

Charcot in 1856 found the same crystals in the expectoration in two cases of catarrh sec with emphysema. In 1861 White¹⁶² named these crystals "Leukosin," affirming their presence in every case of leucæmia. In 1862 Wagner¹⁶³ saw them in the blood of the portal vein of a twenty-five-year-old anæmic woman.

Two years later Friedrich¹⁶⁴ furnished good drawings of these crystals. He pronounced them as identical with those drawn by Foerster and designated them very positively crystals of tyrosin. He saw the crystals in expectorated fibrinous bronchial coagula of a woman aged forty-two. In the same year Huppert¹⁶⁵ also stated his belief that these crystals are by no means rare in leucæmic blood. Later on Boettcher¹⁶⁶ found them in human sperma. Testing them chemically, he formed the opinion that they were albuminous. Kuehne,¹⁶⁷ in 1868, expressed the opinion that these crystals were related to vitellin; Hoppé-Seyler¹⁶⁸ referred to Boettcher's crystals with the remark that they probably correspond to the yolk-scales and the aleuron-crystals of many plants; while Neuman,¹⁶⁹ in 1860, discovered the crystals in the blood of a leucæmic man several hours after the post-mortem.

In 1872, in numerous cases of bronchial asthma, the same crystals were observed by v. Leyden¹⁷⁰ as constituents of the sputum and he declared they were characteristic of this disease, Salkarowski,¹⁷¹ who examined samples of such sputa obtained by v. Leyden, expressed the opinion that they were a crystallised mucin-like substance.

In 1876 Lanenstein¹⁷² found in leucæmia large quantities of these crystals in the bone-marrow and in the mesenteric glands. This communication by Lanenstein is followed by an article by Zenker,¹⁷³ "On Charcot's Crystals in the Blood and the Tissues of Leucæmic Persons and in the Sputis." Thereupon, in 1878, Schreiner,¹⁷⁴ as already mentioned, communicated his observations on the occurrence of the crystals, and to him is due the credit for having demonstrated the chemical identity of these crystals in different organs.

The publications of Prof. Fuerbringer¹⁷⁵ and P. Guttmann,¹⁷⁶ as we have already said, once more aroused doubt as to the chemical identity of the crystals of Spermin and the asthma crystals of Charcot-Leyden. All doubts, however,

are now dispelled, since the publication of the results obtained by Poehl in his very extensive and carefully executed tests.*

From these statements the conclusion is reached that *Spermin* is widely distributed in the male, as well as in the female, organism. This fact on the one hand, and the presence of this body in so large a quantity in the sperma on the other, caused Poehl to suppose that it has an important share in the functions of the organism.

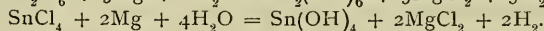
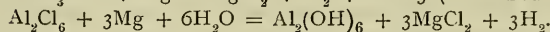
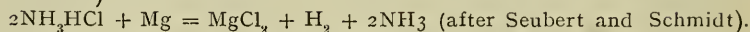
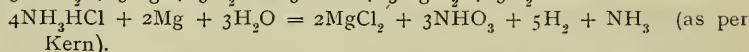
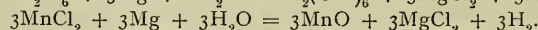
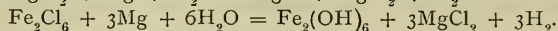
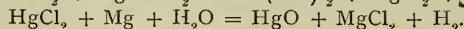
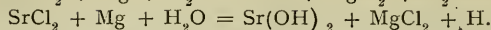
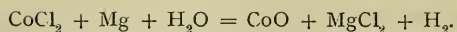
After Poehl had succeeded in isolating *Spermin* in sufficient quantities, he begun his experiments for the determination of the chemical significance of this organic base in the functions of the organism. In the first place, his attention was attracted by the fact that the smell-reaction with magnesium always accompanies the formation of magnesium-hydroxide. He soon satisfied himself that the presence of *Spermin* has a direct influence upon the formation of MgO , respectively $Mg(OH)_2$ during this reaction. This investigation of the magnesium-*Spermin*-reaction had already been made by Poehl¹⁷⁷ before the publication of K. Seubert and A. Schmidt's article "On the Influence of Magnesium on the Chlorides" (Inaugural-Dissert. Tuebingen 1892, cf. *Annalen der Chemie*, 1892 [Bd. 267], pp. 218-249, cf. *Chem. Centralbl.* 1892, I. p. 923).

§ 70. Chemical
reaction of
spermin

The effects of the Chlorides on metallic Magnesium had already been observed by N. Beketoff, Roussin, Comaille, Kern, and Winkler. Seubert and Schmidt demonstrated that by the action of magnesium on chlorides the chlorides of the metals in neutral watery solution give their chlorine to the magnesium. In this reaction, as well with as without, *Spermin*, hydrogen is formed. Poehl, however, satisfied himself that in the presence of *Spermin* the oxidation of magnesium and the formation of hydrogen increase with an increased quantity of chloride of *Spermin*.

The reactions without *Spermin* with formation of $MgCl$ proceed as follows :

* We must, however, call attention to the fact that as late as 1902 at the Congress of Internal Medicine at Wiesbaden (see Transactions of the Congress, pp. 210-218) Prof. Gumprecht, of Weimar, asserted that Charcot-Leyden crystals were crystals of albumen. It was clear from his paper that Prof. Gumprecht was absolutely unacquainted with the chemistry and the literature of the question. It will suffice to quote his first argument: "The double-refraction of the coagulated crystals, treated with corrosive sublimate, has almost entirely disappeared." Sapiienti sat!



§ 71. Katalytic action of oxidation of spermin on metallic magnesium

As to the formation of Magnesium-hydroxide, Seubert and Schmidt (*loc. cit.* p. 246) emphasise the fact that, "as a rule, besides the basic salts and the hydroxides, the hydroxide of magnesium also appears. In the action of the Mg on the chlorides of the noble metals, however, and in that of lead and thallium, magnesium-hydroxide is not formed."

When Poehl, however, produced the Spermin-magnesium-reaction in presence of chloride of gold, the formation of magnesium-hydroxide always occurred and very energetically. In making the reactions with PtCl_4 , as well as with HgCl_2 , CuCl_2 , ZnCl_2 , BaCl_2 , SrCl_2 , NH_4Cl , &c., when comparing the reactions with or without Spermin, the influence of the latter on the oxidation of the magnesium becomes evident. In presence of *Spermin* the formation of magnesium-hydroxide is particularly striking. Very characteristic also is the fact that even very small quantities of *Spermin* have an influence on the oxidation of magnesium (Poehl).

As previously mentioned, the reaction must be made under certain important conditions, when the characteristic sperma-smell always appears. In the performance of the reaction with chloride of ammonium the odour of the ammonia interferes with the perception of the sperma-smell.

As the formation of Mg(OH)_2 takes place at the expense of the oxygen which is set free by the decomposition of the water, Prof. Poehl, for the purpose of measuring the influence of Spermin on this, made some experiments by which the quantity of the hydrogen set free is determined.

The quantity of the freed hydrogen and the length of time taken by the reaction served as guides to Poehl. The result was that the energy of the reaction depended on the quantity of Spermin. The oxidation of the magnesium, however, as well as the volume of the freed hydrogen, remained equal, even with the smallest quantities of Spermin. In short, the oxidation of enormous quantities of magnesium can be accomplished even with very small quantities of Spermin.

Here according to Poehl Spermin operates katalytically, as on the one hand the reaction does not depend on the quantity of Spermin, while on the other, as appears from the following experiment, after the reaction the Spermin remains

apparently unchanged. If the reaction is performed with a diluted solution of CuCl_2 with the addition of much magnesium and little Spermin, care being taken that the warming (which always appears and depends on the energy of the reaction) does not become so great as to destroy the Spermin, the latter can be extracted with water from the remaining mass in an unaltered condition and the filtrate upon the addition of CuCl_2 and Mg, will give the reaction anew.

These observations¹⁷⁹ of Prof. Poehl were communicated to the Paris Academy of Sciences by Prof. Armand Gautier. In the discussion thereupon Prof. Duclaux¹⁸⁰ expressed the opinion that the Spermin might be replaced by some other means, such as saponin, which would offer to the powdered magnesium a great surface on the foam-bubbles. As a result of this objection Prof. Poehl¹⁸¹ made some parallel experiments with Spermin and saponin. The results of these experiments are given in the following table, and show that the objection of Duclaux had no justification in fact.

	I.	II.	III.	IV.	V.
Metallic Magnesium in powder-shape	0.5	0.5	0.5	0.5	0.5
Solution of CuCl_2 ($\frac{14}{1000}$)	4Cc	4Cc	4Cc	4Cc	4Cc
Water	50Cc	50Cc	50Cc	50Cc	50Cc
Spermin	0.04	0.007	0.004	0	0
Saponin	0	0	0	0	0.004
Ccm of H, collected after 24 hours, and reduced on $T=0^\circ$ and $H=760$ mm.	432.52	431.59	432.98	65.80	141.10
Hydrogen received on addition of 3Cc. HCl (spec. grav. = 1.124) made after 24 hours. The tests of the volume reduced to $T=0^\circ$ and $H=760$ mm.	25.84	25.98	26.14	394.24	313.95

Prof. Poehl also made some experiments in which, in place of the powdered magnesium, he used the metal in strips, thus excluding the moments of surface-action, which, according to Duclaux, favour the oxidation of the magnesium. Under steady conditions of the reaction the results were about the same. The energy of the reaction, of course, was less in the experiments with strips of magnesium, that is, the time taken, as was to be expected, was increased.

§ 72. Action
of spermin
on the
processes of
oxidation in
the blood

After Prof. Prince Tarchanoff had observed that animals subsequent to hypodermic injections of *Sperminum-Poehl* were more fit to stand narcosis with chloroform; and after Prof. Weljaminoff, surgeon to his Majesty the Czar, had come to a similar conclusion in the use of *Sperminum-Poehl* in surgical practice, Prof. Poehl¹⁸² instituted a series of experiments for the purpose of learning to what extent Spermin influences the power in the blood to transfer oxygen. The results obtained from these very thorough experiments by Prof. Poehl,¹⁸³ were tabulated and published, and to these the reader is referred. From these observations it became evident that in the cases in which the power of oxidation of the blood was lowered under the influence of different agencies, as, for instance, chloroform, nitrogen monoxide, some pathological constituents of the urine, the function was restored under the influence of *Sperminum-Poehl*, in presence of which the blood did not change spectroscopically.

These experiments also demonstrated that the power of the blood to transfer oxygen was lessened by the addition of an acid.

After the blood has left the organism a decrease of its alkalinity is very soon observable—a fact to which Prof. v. Jaksch¹⁸⁴ long ago called attention. Such a blood will not oxidise benzaldehyd or salicylaldehyd directly. When Poehl,¹⁸⁵ however, added a small quantity of Spermin, benzaldehyd was oxidised to benzoic acid and salicylaldehyd to salicylic acid.

§ 73. Katalysators in the form of oxydases in the organism

As all these experiments show, Spermin plays the part of a katalysator of the processes of oxidation in the organism. Prof. Poehl especially emphasises the fact that in addition to this katalysator others are in the body in the form of oxydases. Doubtless, however, Spermin performs the most important function in the physiological processes of oxidation. Before Poehl, Schmiedeberg¹⁸⁶ had, however, in 1881, such an oxydase in hand. He named it Histozyim, but made no more exact chemical determination. According to the observations of Poehl, Rochmann and Spitzer¹⁸⁷ dealt with the question of oxidising ferments in the organism. Spitzer, from insufficient acquaintance with the work of Prof. Poehl, came to a number of wrong conclusions, which were refuted by Prof. Poehl,¹⁸⁸ as well as by Dr. Cohn.¹⁸⁹ Subsequently Salkowski,¹⁹⁰ Yamagin, Abelous, and Biarnès,¹⁹¹ Jakoby,¹⁹²

Rosell,¹⁹³ Bonrguelot,¹⁹⁴ Bertrand,¹⁹⁵ Medwedjeff,¹⁹⁶ demonstrated the existence of oxydases in the animal organism. M. Jakoby has discussed the question of the intracellular ferments in physiological results. He is, however, insufficiently acquainted with Russian and French literature, and apparently not at all with that on *Spermin*. Still, in spite of this defect, we refer the reader to this work, because we find in it a discussion of the work done on oxydases at Heidelberg in the laboratories of Bredig and Hofmeister.

We will not refer here to the very extensive literature on the oxydases; we will confine ourselves to the discussion of the part taken by Spermin in the organism. The most essential significance of Spermin in the organism is doubtless that it operates as a positive katalysator of the processes of oxidation. The physiological-chemical observations of Prof. Poehl and the clinical experiences of a long series of clinical authorities clearly prove this.

Every irritation of a cell and every function of life are connected with the formation of products of metabolism. The removal of these is one of the objects of textural respiration, that is, the intraorganic oxidation. Without removal of the products of metabolism the functions of the cell are impossible. These compounds very often have direct toxic qualities, and their presence must, of course, cause poisoning of the organism (auto-intoxication).

§ 74. Textural respiration and intra-organic oxidation

Still, some indifferent products of metabolism, when incompletely removed from the cells and tissues, may cause a disturbance of their function, and in this way some auto-intoxications.

To the nitrogenous products of the retrogressive metamorphosis, the collective name of leucomaines has been given by Armand Gautier.*

These leucomaines attract our attention in the first place, because they play a great pathological part in the anomalies of the metabolism.

§ 75. The rôle of the leucomaines in auto-intoxications and how they are rendered harmless by oxidation

Bouchard, Gautier,¹⁹⁷ &c., have demonstrated that the toxic products of metabolism are either rendered harmless by oxidation and hydration or their toxicity is at least essentially

* Armand Gautier at first introduced the name leucomaines for the bases of animal origin only. Subsequently, however, it was used for the ureides as well as the amin-acids of animal origin, in short for all the intermediary nitrogenous products of retrogressive metamorphosis. We shall employ the term leucomaines in the wider sense last named.

diminished. As example we may name, the change of the neurin by oxidation to oxyneurin and cholin. According to Gautier, for the rabbit 0.005 neurin corresponds as regards the toxic effect to 0.1 cholin. The qualitative character of this very strong poison is hereby but little changed. Kreatin, which distinguishes itself in its toxic effect by convulsions is, as well as kreatinin, changed in the organism by oxidation and hydration to the harmless urea.

The very toxic hypoxanthin (according to Gautier,¹⁹⁸ it produces muscular spasm and paralysis of the spinal chord) is changed by oxidation to the less toxic xanthin, and finally becomes the perfectly indifferent compounds alloxan and urea.

Kreatin and xanthin compounds, and similar toxic substances, are excreted with the urine, and in diseases co-existent with decreased processes of oxidation they appear in larger quantities, and cause the toxic qualities of the urine.

Bouchard¹⁹⁹ was the first to demonstrate that by an increase of the processes of oxidation the toxicity of the urine is essentially diminished.

Oxidation has not only the task of making the products of metabolism harmless; by it also the not readily soluble products of the retrogressive metamorphosis are changed to readily soluble compounds. To this action is altogether due the credit of the possibility of the removal of the products of the metabolism from the tissues to reach the general circulation of the juices, to be thence finally eliminated from the organism through the kidneys, the skin, etc.

Under normal conditions, as Armand Gautier²⁰⁰ demonstrated, the tissues in our organism lead an absolutely aerobic life, and are immersed in oxygen-containing and oxidation-promoting juices. When, however, forces appear in the organism which lower the oxidation, then, as Gautier showed, the tissues lead a (facultatively) anaerobic life. These forces give rise to a kind of auto-intoxication which Poehl named auto-intoxication from decreased textural respiration. By experiment Gautier, together with Lando Landi,²⁰¹ has demonstrated that in the anaerobic life of the tissues the formation of the toxic, and not readily soluble, intermediary nitrogenous compounds (leucomaines) increases, much lactic acid is produced, and the higher stages of oxidation of the products of the metabolism are evidenced only in very small quantities.

§ 76. Intra-organic oxidation as a factor of the excretion of the leucomaines from the organism

Bouchard²⁰² has endeavoured to measure the toxicity of urine with his (of late) much attacked urotoxic coefficient. Although the method has some defects, the observations of Bouchard have opened up some essential and novel points of view. The chief fault of the method, viz., the injurious action of the quantities of fluid, might be eliminated, as Poehl has already suggested, by using, in place of the urine, the solution of the nitrogenous intermediary compounds which it contains. The latter are precipitated as phospho-tungstate, and can be brought into each solution after dissociation with BaHO.

§ 77. Prof. Poehl's determination of urotoxicity

Although Spermin is always present in the organism, and though the katalytic action referred to accompanies the physiological processes of oxidation, still, immediately certain pathological events take place, a decrease of the intraorganic oxidation results. At first this fact appeared to Poehl as being in opposition to his assumption of the katalytic action of Spermin. He was soon convinced, however, that the katalytic action of Spermin only takes place under certain alkaline conditions of the juices of the tissues. Now, what are the conditions under which, according to Poehl, the physiological Spermin in the organism is rendered powerless?

§ 78. Pathological decrease of the intra-organic oxidation

Normally the muscular, as well as the nervous tissue, presents a reaction which is only slightly alkaline. The living muscles in all animals, striated as well as non-striated, also possess, when at rest, but a slightly alkaline reaction. The reaction of the living white brain-matter, as well as that of the peripheric nerves, has, according to the investigations of Liebreich, Heidenhain, and Gscheidlen always been found but slightly or not at all alkaline. The grey matter and the ganglion-cells show an inconsiderable acid reaction. According to the investigation of J. Moleschott and Battistini, the acidity of the grey matter is increased when active; while, according to Halliburton²⁰³, the living nervous tissue under normal conditions has an alkaline reaction.

§ 79. Nervous and muscular over irritation as cause of the decrease of textural alkalinity

Funke, Ranke, and Afanasjeff²⁰⁴, have already shown that irritation of the muscular and nervous tissues causes a decrease in the alkalinity and even an acidulation of the tissues.

Liebig²⁰⁵ and Engelhardt,²⁰⁶ and subsequently Wislicenus,²⁰⁷ and others, had already dealt with the question of the nature of the acid originating in the muscle, and showed conclusively that it is essentially an

æthyliden-lactic acid: $\text{CH}_3 - \text{CH OH} - \text{COOH}$, which differs from the common fermentation-lactic acid chiefly by being optically active, which is shown by its turning to the right. The lactic acid of the muscular substance, therefore, is meat-lactic acid or para-æthyliden-lactic acid. Besides this meat-lactic acid Heintz²⁰⁸ has shown that there is also a little fermentation-lactic acid in the muscle. Du Bois-Reymond²⁰⁹ established the fact that consequent on the activity of the muscle the formation of the lactic acid is increased to such an extent that its reaction (as, *e.g.*, in the case of poisoning with strychnia) becomes acid. Further investigations in this direction have also been made by Astaschewsky²¹⁰ and W. Cohnstein.²¹¹ The latter states that after tetanisation in rabbits, as well as after strained muscular labour in dogs running in a treading-wheel, the alkalinity of the blood is evidently decreased.

If a muscle is exsclated from the circulation, it is still possible by simple tetanisation to establish an acidulation,²¹² and consequently an increase of the lactic acid in it. Under such conditions Marcuse,²¹³ as well as Werther,²¹⁴ found in an isolated and tetanised muscle of the frog much more lactic acid than in the corresponding muscle of the non-irritated side. If in a rabbit the ischiadic nerve of one side be cut and the animal be poisoned with strychnia, and immediately after or, better still, during the last convulsion the muscles of the calf of both sides are cut out, those at rest are found to be neutral, while the tetanised ones show a most pronounced acid reaction.²¹⁵ In more recent experiments Gotschlich²¹⁶ has succeeded in discovering noticeable acidulation of isolated frog-muscles after electric irritation of so slight a character that no visible contractions were produced.

H. Dreser²¹⁷ has shown that this fact can be demonstrated in another way:

If two or three times during the twenty-four hours a Pravaz syringe of the comparatively harmless five-per-cent. acid-fuchsin is injected hypodermically into frogs, their muscular system will be charged sufficiently with the stain, which lies in the lymphatic fissures between the muscular fibres. The inactive muscles, on account of their alkalinity, will then show no, or but very little, rose-colouring. If, however, after interruption of the circulation (with a view to avoiding the neutralisation of the acid originating in the active muscle) the ischiadic nerve of one side is intermittently irritated tetanically, for from ten to fifteen minutes, a vivid redness appears in the irritated thigh. This must be considered as proving the formation of acid in the active muscle.

Berzelius²¹⁸ appears to have shown already that the perfectly fresh muscles of game hunted to death have an acid reaction. The nature of the acid appearing on irritation of the brain and the nervous system, as well as during the changes after death, has been carefully sought for by many observers. Lactic acid was discovered in the brain, first by Bibra, then by W. Mueller.²¹⁹ A volatile organic acid was also found which, with nitrate of silver, acted like formic acid. The lactic acid in the brain, according to Gscheidlen, proved to be fermentation-lactic acid. As far as the formation of lactic acid in the brain is concerned there is an analogy to the muscular tissue. In the former, however, fermentation-lactic acid (inactive æthyliden-lactic-acid) is chiefly formed, while in the latter meat-lactic acid (active æthyliden-lactic acid or paralactic acid) is produced.

The substance of the brain, as well as the spinal cord, can be acidulated

by other agents than irritation. According to Gscheidlen, if the white substance be warmed to from 45° to 50° C. the alkaline reaction is changed to the acid and the degree of acidity in the grey substance is increased. Further, the grey substance is naturally neutral, as Gscheidlen has established by the following very interesting experiment: He washed out the brains by injection of a 0.6-per-cent. solution of common salt into both carotid arteries, when the grey substance proved of neutral reaction.

In 1900 Poehl²²⁰ recognised—in a communication made to the International Medical Congress in Paris, “*Les auto-intoxications par surfatigue des tissus nerveux et musculaires et leur traitement par l’organotherapie*”—that the accumulation of the lactic acid formed by over-irritations of the nerves causes the physiological spermin to become inactive. More: in this case a *circulus vitiosus* takes place, as on the one hand the acidulation of the textural juices decreases the processes of oxidation, while, on the other, in consequence of the decreased oxidation, the lactic acid is not, as under normal conditions, burnt to CO₂, but produces, by accumulation in the textural juices, an acidulation of the latter. Under normal conditions Spermin is prevented from becoming inactive by the fact that the tissues are immersed in the alkaline textural juices. When, however, the irritation of the tissues is prolonged, either the formation of acid in the tissue affects the alkalinity of the blood in the whole organism and decreases it, as Cohnstein (*loc. cit.* § 79) demonstrated in overtired dogs, or a local acidulation of the irritated tissue or organ appears. Poehl believes that the latter condition arises from the formation of products with acid reaction, which are either not easily soluble or dispersed and therefore remain in the tissue.

The katalytic action of Spermin on the intraorganic oxidation cannot take place under these conditions. The products of the retrogressive metamorphosis cannot be changed to compounds that are readily soluble and diffusible, and hence they accumulate in the tissues of the organism. The toxic leucomaines which, as we have seen, lose their toxicity by oxidation, remain in the organism during their toxic state, while the indifferent leucomaines, being foreign bodies, charge the cells and tissues and so disturb their functions.

It is easy to understand that in this way the manifold pathological symptoms are produced which Poehl named “Auto-intoxication from decreased intraorganic oxidation”²²¹. He has demonstrated by urinalyses that in a very great number

§ 80. How spermin is rendered inactive by a decrease in the alkalinity of the blood

§ 81. Auto-intoxication from decreased intra-organic oxidation

of diseases an accumulation of leucomaines takes place in the organism. He points out that in acidulation of the textural juices agents exist for the formation of phosphate of Spermin, which is not readily soluble, whereby active Spermin changes to an insoluble compound, and consequently loses its katalytic action. In the organism the amorphous²²² phosphate of Spermin is chiefly formed, though the crystals, which are known as Charcot-Leyden's, often appear here.

The crystals of phosphate of Spermin have always been found in such diseases as are associated with decreased intraorganic oxidation. *v. Leyden*, *v. Jaksch*, and others, have found these crystals in the sputum of asthmatic persons; while *Charcot*, *Robin*, *Vulpian*, and *Neumann* have seen them in the blood of leuchæmic ones. According to *Nothnagel*, *Leichenstern*, etc., they have been found too in typhoid fever, pneumonia, and phthisis.

The effect of the intraorganic oxidation of the active Spermin which normally occurs in the organism, does not confine itself to the nitrogenous products of the retrogressive metamorphosis. It extends also to the fats, the carbohydrates, the aromatic compounds, etc. We have, as we have shown, experimentally established the oxidising action of Spermin in the presence of blood on benzaldehyd, salicylaldehyd, etc. It is therefore to be expected that the active Spermin in the organism exercises an oxidising influence on the lactic acid, and in this way prevents the acidulation of the tissues. The investigations of Profs. *Senator*, *Loewy*, and *Richter* afford sufficient evidence of this fact. Further, the very careful investigations of *F. Chvostek*²²³, in his "Ueber den oxydativen Stoffwechsel bei Sacureintoxication," besides those of others, provide evidence that the acidulation of the tissues from the cessation of the activity of the Spermin decreases the processes of oxidation in the organism. In rabbits which were poisoned with acids, *Chvostek* discovered the exchange of gas and the loss of heat, and in this way demonstrated a decrease of the processes of oxidation. As *Walter*²²⁴, has shown that the blood of animals poisoned with acid contains a normal amount of oxygen, *Chvostek* acted on the assumption that through poisoning with acid the tissues lose their capability of holding oxygen. He compares this loss of the protoplasma's capability of taking up O with a "textural asphyxia," as *Geppert* has

proved is the case in poisoning by prussic acid. This "textural asphyxia" corresponds perfectly with the decrease of the textural respiration from the cessation of the activity of the Spermin.

One of the auto-intoxications, which are caused by acidulation of the tissues and decrease of the intraorganic oxidation, produces an accumulation of uric acid in the organism.

In pathology these forms of disease are known as uric acid diathesis" or "uratic diathesis." With less reason, however, other diseases are admitted to this group, by which xanthin-compounds and not uric acid are accumulated in the body.²²⁵

§ 82. Uric acid diathesis as auto-intoxication from decreased intraorganic oxidation

The uric acid, as well as the xanthin, diathesis is mainly caused by factors which produce an acidulation of the tissues, and it depends on the nature and the physiological rôle of the tissues affected to decide which disease originates.

Prof. Poehl, in an article entitled, "The Action of Spermin on the Metabolism in Auto-intoxications generally, and in Uric Acid Diathesis especially," has thoroughly discussed the physiological-chemical side of the question of the uratic diathesis. Therewith he endeavoured to explain the difference between the results obtained by Horbaczewski and Kossel concerning the decomposition of nuclein.

According to the theory of Horbaczewski uric acid and xanthin-bases are formed from mutual previous stages, the former, if these previous stages are first oxidised, the latter, if they are split without oxidation. Therefore, if the processes of oxidation are normal, the quantity of the xanthin-bases will be smaller, as they are oxidised to uric acid, or to some higher product.

As evidence for the dependence of the character of the products of the retrogressive metamorphosis upon the energy of the intraorganic oxidation we call attention to an experiment of Horbaczewski²²⁶. He showed that different organs, when blood was artificially passed through them, gave to it some uric acid and xanthin-bases. When the blood was kept arterial by the addition of sufficient oxygen, the formation of uric acid was materially increased, while when venous blood was employed xanthin-bases alone were present. From these experiments the influence of the oxidation is evident, and is in perfect accord with the above-mentioned assumption of Poehl.

§ 83. Formation of uric acid by decomposition of nuclein

Consequently uric acid is one of the products of decomposition of the nuclein-containing elements in the organism. Seeing that, as a rule, according to Horbaczewski,²²⁷ in addition to certain epithelia, leucocytes chiefly are decomposed, the formation of uric acid is mainly dependent upon the number of these to be decomposed. In many pathological conditions, which accompany decomposition of tissue, uric acid also originates from the disintegrating textural elements. Examination of the formation of uric acid in different pathological conditions shows that all those diseases which are connected with decomposition of nuclein-containing tissue (leuchæmia, phosphor-poisoning, acute feverish diseases, especially pneumonia, cachexia, cirrhosis of the liver, burns and scalding of the skin, pernicious anæmia, etc.) are also remarkable for an increased excretion of uric acid.

All the above-mentioned diseases, according to Poehl, are also characterised by a lowered intraorganic oxidation and a decreased alkalinity of the blood, and they are all pronounced auto-intoxications. We see, therefore, that the increase in the formation of uric acid in these diseases is intimately connected with the forces already mentioned.

§ 84. Uric acid as a cause of disease

Haig²²⁸ has accounted for attacks of gout, rheumatism, hemicrania, epilepsy, mental depression, etc., by the retention of uric acid. Herter and E. Smith²²⁹ made special investigation into the causes of chorea, epilepsy, neurasthenia and hemicrania. In four cases of chorea they found a large increase of uric acid in the urine, but as the patients improved there was a gradual reduction in it. In epilepsy they agree with Haig that the attacks are usually followed by an increased excretion of uric acid, which is sometimes strongly marked on the second day only. They could not, however, confirm the decrease of the excretion which, according to Haig, precedes the attacks. In the "petit mal" they found a continual increase of uric acid in the urine, which became less as the symptoms abated. In neurasthenia a relative increase of uric acid is the rule; only in one case out of nine was it not markedly evident.

In all the cases referred to the increase in the formation of uric acid was complicated with decreased intraorganic oxidation. The uric acid, however, is not only increased because the oxidation is decreased, but because the decay of the nuclein-

substances apparently takes place under abnormal conditions, that is, in an acid medium. According to Poehl, therefore the decreased alkalinity of the blood and the lowering of the intraorganic oxidation form a *circulus vitiosus*, both factors being related to each other as cause and effect ; besides which both operate in the same direction.

Ruedel²³⁰ has found that the excretion of uric acid from the organism depends upon the formation of urea, because urea alone is capable of keeping uric acid in solution and of carrying on the excretion. According to him the uric acid is present in the urine as a union of uric acid and urea in molecular proportion (urea + uric acid + H_2O). In this way Ruedel also explains why a surplus of acid must always be taken for the precipitation of uric acid, when the separation of the sediment proceeds slowly.

The explanation of the action of alkalies on the excretion of uric acid, as given by Clar and Haig, is not quite correct, because both authors attach chief importance to the alkali which circulates. In their opinion, this washes out the tissue in which an accumulation of the uric acid has taken place. Poehl, states, however, that the effect of the alkalies in uric acid diathesis is to bring the alkalinity of the blood to the normal. In this way Spermin becomes active, and the processes of oxidation are increased. Some uric acid is consequently oxidised to urea while the residue is excreted as uric-urea-compound.

Still, as we shall see, the therapeutic action of *Spermin* is very much the same as that of the alkalies in general, and the alkaline mineral waters especially. The difference is only in the energy and swiftness, which are greater in Spermin than in the alkalies. It is also easy to understand that by the simultaneous employment of alkalies during treatment with *Spermin* the quickest possible effect is obtained, as has already been empirically established by Hirsch, Physician to his Majesty the Czar, Rostchinin, Prof. Lauder-Brunton, Symons-Eccles, etc.

We have already stated that *Spermin* originates from the disintegration of nuclein, and that it remains active only if the normal alkalinity of the blood is maintained. The old therapeutic method of the fontanel, the curative effect of which has been established beyond doubt in some cases, is, according to Poehl, also based on an increased disintegration of leucocytes and the formation of Spermin which accompanies it.

Prof. E. v. Leyden²³¹ first recognised the connection between the appearance of eosinophile cells and the crystals of phosphate of Spermin. This phenomenon is also explained by Poehl, who says that we have here to deal with a disintegration of the eosinophile cells, that is, of elements rich in nuclein, in a decreased alkalinity of the blood. An article which Prof. v. Leyden published in 1891 contains a passage which we reproduce *in extenso*, because the factors in the formation of

§ 85. Formation of phosphate of spermin upon the decomposition of leucocytes in an acid medium

Charcot-Leyden's crystals, as they are clearly expressed in this article, agree exactly with the factors causing the cessation of the activity of *Spermin*, as they are enumerated by Poehl. Prof. v. Leyden says :

"As to the relation of the asthma-crystals to the eosinophile cells, I believe that it may be said that a certain connection must exist between them, because, to judge from the investigations so far made, they are nearly always found together. The crystals originate in the bone-marrow and the juice of the spleen. Especially from leucæmic blood they can be gained quickly and abundantly and always from places where leucocytes are glued together, but not from between the erythrocytes. Therefore a relation between the eosinophile cells and the crystals can hardly be denied. Hence, it seems to be, that the simultaneous recurrence of crystals and eosinophile cells in the asthmatic is also striking and remarkable and although till now there are but few cases which I can report, it is doubtless a fact that both appear about the same time and in part disappear again, when the asthmatic spell is over. In the other cases I observed that the number of the eosinophile cells, though not absolutely depending upon the number of the crystals, still stands in a certain general porportion to them."

With the connection between eosinophile cells and *Spermin* we shall yet have to deal when discussing the question of immunity.

We have made ourselves acquainted with the physiological-chemical action of *Spermin*, and will now proceed to consider how it acts therapeutically on the disturbed, that is, the pathological, metabolism. According to Poehl *Sperminum-Poehl*, whether given per os, or hypodermically, or per clysm, if administered under equal conditions, influences the metabolism in the following way :

§ 86. Influence of *Sperminum-Poehl* on the metabolism, and relatively on the coefficients of urine

(1) The proportion of the urea-nitrogen to the total of the nitrogen in the urine after the employment of *Spermin* comes nearer to the unit, that is, the quantity of the urea-nitrogen rises.

The increase of this co-efficient of oxidation is accelerated in all methods of administration, if the alkalinity of the blood is increased simultaneously by the use of proper medicines, brought respectively to the normal. In diseases in which the pulmonary oxidation is diminished, the co-efficient of oxidation cannot be raised to the normal even by the use of *Spermin*, because, about 80 per cent. of the processes of oxidation proceed at the expense of the oxygen inhaled by the lungs, while less than twenty per cent. devolve upon the intraorganic oxidation.

The increase of the co-efficient of oxidation is coincident with the appearance of the leucomaines in the urine, and the influence of Spermin shows itself in a twofold manner: first, there is a direct increase of the urea with a simultaneous decrease in the quantity of the leucomaines; and, secondly, in the beginning a decrease in the quantity of the leucomaines, without any great change in the quantity of the urea, followed by an increase of the urea with a simultaneous decrease of the leucomaines.

These phenomena agree perfectly with the oxidising action of *Spermin*. After an accumulation of the leucomaines has taken place in the organism, they undergo in the first place such changes by oxidation as render them fit to pass over from the tissues into the circulation. By further oxidation these changes may be continued up to the formation of urea. Hence, in the first case the quantity of the leucomaines will be increased without an increase in the amount of the urea, while in the second case the quantity of the urea in the urine increases simultaneously with a diminution in the quantity of the leucomaines. Be that as it may, however, we have in both cases to deal with an increase of the processes of oxidation, while in both instances the organism reaches a similar result as the tissues are freed from leucomaines.

(2) According to Prof. Poehl the proportion of the urea-nitrogen to the total nitrogen of the urine becomes practically normal by the therapeutic employment of *Sperminum-Poehl*, that is the quantity of nitrogen in urea increases, while that of the intermediary products decreases.

§ 87. Action of Sperminum-Poehl on the coefficient of the energy of oxidation

This is confirmed, among others, by the following observations. Rossi²³² found in one case of scurvy, in which the proportion of the total nitrogen to that of the urea was = 100 : 84.25, after thirteen injections of *Sperminum-Poehl*, this proportion increased to 100 : 93.32. From Rossi and Gretschaninoff²³³ we have: (1) Scurvy. From May 21 to June 15 fifteen injections of Spermin. Before the injections the proportions were 100 : 85.21 and 100 : 86.14; after them, May 24 and 26, 100 : 91.33 and 100 : 92.60. (2) Scurvy. From May 10 to 18, seven injections; before them = 100, 87.23, increased during the use of Spermin to 100 : 93.78. Fleroff and Gretschaninoff²³⁴ give: Scurvy. From February 10 to 18, six injections. The urinalysis of February 12 gave the proportion as 100 : 86.42, on February 24 it was 100 : 92.28. Gretschaninoff²³⁵ gives four cases of scurvy; (1) from April 26 to May 13 thirteen injections. Before them the proportion was 100 : 92.31; after them on May 2 it was 100 : 93.2. (2) From July 5 to 18, nine injections. Urinalysis on July 5 gave the proportion as 100 : 90.33; after the injections, on July 20 it

was 100 : 92.38. (3) Before the injections the proportion was 100 : 91.47, and after them, July 5, 100 : 92.36. (4) From April 16 to May 24 nineteen injections. On April 23 the analysis gave the proportion as 100 : 84.24; on May 4 after the injections as 100 : 90.24. Profs. Afanassieff and Schapiro²³⁶ give arthritis deformans. From February 17 to July 15, thirty-seven injections. Analysis of February 12 gave 100 : 85.78; on May 8, after the injections 100 : 92.56. Prochoroff²³⁷ gives: Arthritis chron. Patient took *Essentia Spermini-Poehl* per os, from February 10 to 28. On February 7 the proportion was 100 : 83.28. Analysis of March 3 gave 100 : 90.16. Rossi²³⁸ obtained the following results from treatment with Spermin, of soldiers sick with cholera asiatica : (1) Soldier K—off, five injections July 22, injection of Spermin, the proportion was 100 : 83.29. August 3, injection of Spermin; the proportion was 100 : 93.18. (2) Soldier S—ko. On the first day, one injection. then for five days three injections per day; August 10, before the treatment, the proportion was 100 : 83.55; after it, on August 16 it rose to 100 : 92.37. (3) Soldier Gb—witsch. In the course of three weeks ninety-seven injections of Spermin. In the beginning of the disease the urinalysis gave a proportion of 100 : 82.15, which during the re-convalescence rose to 100 : 92.43. Cohn²³⁹ obtained in three consumptives the following numbers: (1) Before the use of Spermin, the proportion was 100 : 83.13; after twenty-four injections it rose to 100 : 91.81. (2) Before the use of Spermin, the proportion was 100 : 82.27; after twenty-four injections it rose to 100 : 90.23. (3) Before the use of Spermin, the proportion was 100 : 90.29; after twenty-four injections it was 100 : 91.17. In a case of anæmia and neurasthenia the favourable influence of *Sperminum-Poehl sicc. pro clysm.* on the metabolism and the processes of oxidation in the organism was established. After four clysms the coefficient rose from 100 : 76.37 to 100 : 90.34. Schulin²⁴⁰ also satisfied himself in a considerable number of diseases that the lowered coefficient of oxidation is increased by the hypodermic injections of *Sperminum-Poehl*, as well as by the internal use of the *Essentia Spermini-Poehl*. He gives the following examples : (1) Partial paralysis of the left side. July 15, the coefficient was down to 80. After fifteen hypodermic injections of *Sperminum-Poehl* (three injections daily for five days), on July 21 an increase of the coefficient to 89.472 was found. (2) Asthenopia and slight nystagmus. Hypermetropia (+ 2.00 and + 3.00 D.). Vision a little below the normal $\left(\frac{20}{25}\right)$. Under the influence of *Essentia Spermini-Poehl* the coefficient rose from 83 to 88. (3) Progressive muscular atrophy; injections of Spermin for two weeks, one ampulla per day. Coefficient of oxidation; before the injections was 100 : 77.33; after them 100 : 83, and two weeks later it was 100 : 94.15; and on February 18, after two injections, the coefficient was 100 : 90.75.

§ 88. Action of *Sperminum-Poehl* on the coefficient of vital energy

(3) The proportion of the quantity of urea to that of the chlorides according to Prof. Poehl changes during the use of *Sperminum-Poehl* according to the increase in the amount of the latter used.

The following data may serve as evidence for the action of *Sperminum-Poehl* on the vital energy. Dr. Podkopajeff²⁴¹ found after the use of *Sperminum-Poehl* in a case of pulmonary tuberculosis an increase of the

co-efficient of the vital energy. The proportion of the urea to the NaCl was on May 3 = 10.8 : 3.33, relatively 100 : 31.8 ; on June 3 it was 13.00 : 5.74 relatively 100 : 44.2 ; on June 16 = 6.35 ; 2.87, relatively 100 : 45.4 ; and finally on November 21 it was 11.80 : 14.04, relatively 100 : 114.1. Dr. M. Prochoroff²⁴² observed in a case of arthritis urica an increase of this coefficient. Before the injections of Spermin, on February 7, the coefficient was 15.37 : 9.74, relatively 100 : 63.3 ; on March 3, after the injections of Spermin, the coefficient rose to 11.0 : 12.16, relatively 100 : 110.55. Drs. Rossi and Gretschaninoff²⁴³ found an increase of the coefficient in a case of scurvy. Before the injections of Spermin it was 6.79 : 6.22, relatively 100 : 91.6 and 8.00 : 4.04, relatively 100 : 50.5. After the injections the coefficient was first 13.77 : 4.64, relatively 100 : 33.7, and then 10.36 : 9.96, relatively 100 : 96.1. In another case the same authors found the coefficient of the vital energy on May 9, 33.21 : 15.92, relatively 100 : 68.6 ; on May 10 after the injections of Spermin 23.21 : 20.82, relatively 100 : 86.7 ; on May 15, 15.60 : 16.18, relatively 100 : 103.7. Drs. P. Fleroff and W. Gretschaninoff²⁴⁴ give : Scurvy. The proportion of the urea to the NaCl on February 12 was 23.58 : 9.64, relatively 100 : 40.9 ; on February 24 it was 12.29 : 12.74, relatively 100 : 103.7, etc. etc. During the use of *Sperminum-Poehl sicc. pro clysm.* in a case of anæmia and neurasthenia the coefficient of the vital energy rose from 44.5 to 57.3.

(4) The proportion of the total quantity of the phosphoric acid in the urine to the quantity which it contains as dinatrium-phosphate changes according to Prof. Poehl by the use of *Sperminum-Poehl* in proportion to the increase of the quantity contained in the shape of dinatrium-phosphate.

§ 89. Action of *Sperminum-Poehl* on the co-efficient of the alkalinity of the blood

The following observations confirm this : Dr. Wichert²⁴⁵ found in a case of anæmia a decrease in the alkalinity of the blood to 100 : 34.1. After twelve injections of *Sperminum-Poehl* Poehl-Leyden's coefficient of the alkalinity of the blood was normal. Dr. Rossi²⁴⁶ observed, for instance, in a case of cholera asiatica that before the injections of spermin on July 10 the coefficient of the alkalinity of the blood was 100 : 45.6 ; after ten injections of *Sperminum-Poehl*, on July 14 it had risen to 100 : 68.6. After three more injections, on July 16, it was as high as 100 : 70.3. Rossi also found in another case of cholera asiatica an increase of the same co-efficient under the influence of *Sperminum-Poehl*. On July 22 the proportion was 100 : 46.9 ; on August 3 it was 100 : 57.1. Dr. Ulrich²⁴⁷ observed in a case of ischias before the injections of Spermin on November 13 that the co-efficient was 100 : 50.0. On November 27, after the use of *Sperminum-Poehl*, it was 100 : 76.6. Dr. Prochoroff²⁴⁸ observed a case of arthritis urica. Before the injections of Spermin, on February 7, Poehl-Leyden's coefficient was 100 : 48.4. After the use of *Essentia Spermini-Poehl*, on April 6, it rose to 100 : 54.9. By the use of *Sperminum-Poehl sicc. pro clysm.* in a case of anæmia and neurasthenia after four clysms in the course of six days, Poehl-Leyden's coefficient was raised from 100 : 39.2 to 100 : 67.2, etc. etc.

(5) The proportion of the quantity of uric acid to that of phosphoric acid in the form of dinatrium-phosphate, according

§ 90. Action of *Sperminum-Poehl*

on the co-
efficient of
Zerner

to Poehl, approaches the normal after the use of Sperminum-Poehl.

As evidence of the favourable influence of Sperminum-Poehl on the co-efficient of Zerner the following example will serve: Dr. Rossi²⁴⁹ observed in a case of cholera asiatica a change of Zerner's coefficient. On July 22 the proportion was 0.80 and on August 3, 0.38. In another case he also observed a similar favourable effect follow the use of Spermin. Before the injections, on July 10, the coefficient was 0.99 and after thirteen injections, on July 16, it was 0.46. In a third case the proportion was: Before the use of Spermin, 2.00; then it improved and finally remained, after further injections, at 0.29. Dr. Hildebrandt²⁵⁰ observed a case of typhoid fever. Before the injections the coefficient was 0.68; after the injections 0.55. By the use of *Sperminum-Poehl sicc. pro clysm* in a case of anæmia and neurasthenia, after four clysms the coefficient changed from 0.80 to 0.42.

§ 91. Action
of Sper-
minum-Poehl
on the
osmotic
urinary
coefficient

(6) The osmotic urinary co-efficient is also raised under the influence of *Sperminum-Poehl* in connection with the increase of the intraorganic oxidation.

Concerning the osmotic urinary co-efficient, we refer to the lists which are arranged in tables in the article of Prof. Poehl Осмотическое давление соковъ организма и отношение его къ возникновению и устранению болѣзней, from the Wratsch, No. 34.

The number of thorough clinical urinalyses which Prof. Poehl made on patients under the influence of Spermin, and in which all the above-mentioned urinary co-efficients were determined, is a very large one. For many of these analyses the histories of the diseases also exist. As instance, for Docent Dr. Romanowski²⁵¹ alone more than 3000 urinalyses have been made by Prof. Poehl. Dr. Romanowski also possesses the histories of the diseases.

The explanation of the action of *Sperminum-Poehl* on the osmotic co-efficient is given by Prof. Poehl in his communication to the Paris Academy of the Sciences in 1899: "It appears that in our organism the processes of oxidation are not only a source of energy in the form of heat which is measured in calories; they are at the same time a source of strong kinetic force which is produced in the shape of osmotic force, and is measured by atmospheric pressure. Prof. Poehl reached this conclusion as to the influence of the oxidation on the osmotic tension in the organism by observing the action of *Sperminum-Poehl* on the metabolism. The molecule of albumen is a giant-molecule (according to Schichkoff

more than 30,000), which by oxidation and hydration is split into an enormously large number of molecules of a substantially smaller molecular weight (as, for instance, urea = 60). The osmotic qualities of the molecule of albumen are about equal to zero. By the oxidation the osmotic pressure is increased many times in proportion to the increase in the energy of the processes of oxidation. Further, the electric conductivity is increased simultaneously by the appearance of electrolytes.

In the clinics of Prof. Senator the co-efficient is used which represents the proportion of the N of the uric acid to the total nitrogen of the urine. This co-efficient, as well as others, has been used by Dr. P. F. Richter²⁵² to test the action of *Sperminum-Poehl* on the formation of uric acid. From these highly interesting investigations in the clinics of Prof. Senator, Richter also determined the number of the red and white blood-corpuscles in the blood simultaneously with the urinalysis.

A case of splenic leuchæmia was from August 18 treated partly within injections of *Sperminum-Poehl*, and partly with internal doses of *Essentia Spermini-Poehl* (fifteen drops three times a day).

§ 92. Prof. Senator's observations on the action of *Sperminum-Poehl* on the composition of the blood and on the urine

Quantity of urine.	Spec. gravity.	Number of the blood-corpuscles.				Total N of the urine.	Uric acid.	Proportion of uric acid N to total N of urine.
		Before the injection of spermin.		Two hours after the injection.				
		White.		Red.				
2250	1.018	August 16.				12.993	1.442	1 : 27
		— —						
2800	1.019	August 17.				13.91	1.33	1 : 31
		206000		2136000				
		August 18 : One injection of Sperminum-Poehl.						
		Before injection.		Two hours after.				
2600	1.015	White.	Red.	White.	Red.	13.65	1.406	1 : 29
		224000	—	188000	—			
		August 19 : One injection of Sperminum-Poehl.						
2380	1.011	196000	2140000	128000	2440000	14.827	1.26	1 : 35

Quantity of urine.	Spec. gravity.	Number of the blood-corpuscles.				Total N of the urine.	Uric acid.	Proportion of uric acid N to total N of urine.
		Before the injection of spermin.		Two hours after the injection.				
		August 20: One injection of Sperminum-Poehl.						
		White.	Red.	White.	Red.			
2200	1.017	160000	2740000	104000	2048000	12.406	1.078	1 : 35
		August 21: One injection of Sperminum-Poehl.						
2450	1.016	164000	2720000	106000	2430000	13.977	1.752	1 : 24
		August 22: One injection of Sperminum-Poehl.						
2250	1.011	158000	2640000	126000	2300000	16.38	1.444	1 : 34
		White blood-corpuscles.		Red blood-corpuscles.				
		August 23: Use of Spermin was stopped.						
2500	1.055	136000		2750000		14.77	1.612	1 : 27
		August 24.						
2000	1.018	121000		3044000		16.171	1.51	1 : 32
		Blood-corpuscles		Blood-corpuscles				
		White.	Red.	White.	Red.			
		August 25: One injection of Sperminum-Poehl.						
2250	1.014	188000	3156000	136000	2780000	14.64	1.47	1 : 30
		August 26: One injection of Sperminum-Poehl.						
2000	1.017	—	—	—	—	12.11	0.81	1 : 48
		August 27.						
2700	1.013	—	—	—	—	16.94	1.304	1 : 39
		August 28.						
2250	1.017	136000	—	—	—	15.868	1.2195	1 : 23
		Another series of experiments commenced September 5.						
		September 5: The same diet.						
3500	1.012	196000	—	—	—	13.72	1.217	1 : 34
		September 6.						
2850	1.014	188000	—	—	—	12.56	1.309	1 : 30

Quantity of urine.	Spec. gravity.	Number of the blood-corpuscles.		Total N of the urine.	Uric acid.	Proportion of uric acid N to total N of urine.
		Before the injection of spermin.	Two hours after the injection.			
4100	1.012	September 7: One ccm. Sperminum-Poehl injected. 204000 — 140000 —		12.983	0.8815	1:43
3600	1.013	September 8: One ccm. Sperminum-Poehl injected. 188000 — 136000 —		13.356	0.756	1:53
2600	1.013	September 9: One ccm. Sperminum-Poehl injected. 140000 — — —		13.46	0.897	1:46
2880	1.015	September 10: One ccm. Sperminum-Poehl injected. 124000 — 108000 —		16.12	1.2518	1:39
2350	1.017	September 11. 154000 — — —		15.12	1.44	1:31
2250	1.017	September 12. 168000 — — —		14.143	1.534	1:28

From the number of other cases treated with *Sperminum-Poehl* Richter publishes a case of grave anæmia (Pat. Q.). The values for the excretion of uric acid formed themselves under the influence of the internal use of *Essentia Spermini-Poehl* in the following manner:

Date.	Quantity of urine.	Specific gravity.	Number of the leucocytes.	Total nitrogen of the urine.	Uric acid.	Proportion of the N of the uric acid to the total N of the urine.	Remarks.
October 6	3400	1.010	34800	7.97	0.646	1:37	Three times a day fifteen drops of Essence of Spermin.
„ 8	3000	1.010	38400	8.19	0.301	1:80	
„ 9	2300	1.014	41200	10.46	0.471	1:67	
„ 10	3500	1.014	40800	9.89	0.367	1:80	
„ 11	2950	1.011	29250	6.661	0.441	1:45	

While an immediate influence on the amount of the leucocytes in the urine from the internal use of *Essentia Spermini-Poehl* cannot be demonstrated, it was clearly apparent in the following cases which were treated with hypodermic injection of *Sperminum-Poehl*.

Patient W., Lues hepatica. Secondary anæmia; very great diminution of the amount of the red blood-corpuscles and of the hæmoglobin; from time to time hyperleucocytosis. The investigations made during such a period gave the following results. (The diet remained during the time of the experiments the same as before.)

Quantity of urine.	Spec. gravity.	Number of the blood-corpuscles.		Total N of the urine.	Uric acid.	Proportion of uric acid N to total N of urine.
		Before the injection of spermin.	Two hours after the injection.			
		White.	Red.			
2000	1.011	September 6. 22000	153000	8.54	0.53	1 : 48
2200	1.009	September 7. 18450	136000	7.77	0.397	1 : 59
		September 8 : One ccm. Sperminum-Poehl injected.				
		Before injection of Spermin.	Three hours after injection.			
2250	1.011	White. 1620	Red. 165000 9980 1340000	7.69	0.547	1 : 42
		September 9 : One ccm. Sperminum-Poehl injected.				
		After injection.				
2300	1.010	14400	114000 8000 1640000	7.145	0.667	1 : 32
		September 10 : One ccm. Sperminum-Poehl injected.				
		Two hours after injection.				
2250	1.010	—	— 6180 2080000	7.906	0.337	1 : 70
		Leucocytes.	Erythrocytes.			
		September 12 : Use of Spermin stopped.				
1750	1.010	11328	1860000	5.083	0.36	1 : 42
		September 13.				
2600	1.009	9880	1650000	8.45	0.64	1 : 40
		September 14.				
2750	1.010	—	—	7.984	0.683	1 : 35

The observations of Richter demonstrate that the formation of uric acid is coincident with the disintegration of the leucocytes. These observations, as well as others, demonstrate that hypodermic injections of *Sperminum-Poehl* and the internal use of *Essentia Spermini-Poehl* have similar effects on the metabolism.

CHAPTER V

ANIMAL EXPERIMENTS AND CHEMICAL—PHYSIOLOGICAL EVIDENCE FOR THE ACTION OF SPERMINUM-POEHL ON THE INCREASE OF IMMUNITY AND ON THE EXTINCTION OF THE TOXICITY OF THE TOXINS.

§ 93. Evidence for the harmlessness of Sperminum-Poehl administered hypodermically in large quantities into the blood of animals

THE first experiments as to the action of *Sperminum-Poehl* on the animal organism were made by Prof. Prince Tarchanoff and were mainly demonstrated to the Society of Russian physicians at St. Petersburg on February 7, 1891.²⁵³

In small and moderate doses (0.01–0.04 grm.), *Sperminum-Poehl*, when given hypodermically to frogs, has a weak general effect. This is shown by the calmness of the animals experimented on, by a slight decrease of the respiratory movements, as well as of the action of the heart. Further, with an unchanged or little weakened acid-reflex, an increase of the tactile reflexes was observed. After several hours this effect disappeared without leaving any traces. Neither in birds, nor in mammalia (dogs, rabbits, and guinea-pigs), was any immediately noticeable effect observed, after the administration of similar doses.

On doses of from 0.04 to 0.05 grm. being used a more distinctly marked depressing effect always appeared in frogs, taking the form of an intense weakening of the acid and tactile reflexes, an immobility of the animals operated on, a much retarded respiration, and a less pronounced retardation of the heart-action. The continuance of this condition was proportionate to the amount of Spermin introduced. In frogs, however, even when larger doses (0.3 grm. Spermin) were used it did not cause death. Rabbits, dogs, and guinea-pigs easily stood doses of 0.4 grm. even on direct introduction into the blood. Mammalia, however, showed no symptoms of depression whatever, while in pigeons the administration of doses of 0.2 grm. and over produced drowsiness; though even these symptoms disappeared after a time.

It therefore becomes evident that *Sperminum-Poehl* has no

toxic qualities whatever. It further appears that on healthy animals *Spermin* acts so indifferently that it may be almost considered absolutely harmless, even when large quantities are introduced into the blood. As *Spermin* is a normal physiological constituent of the blood, its indifferent conduct towards the organism is easily understood. This fact and the results of his observations induced Prof. Prince of Tarchanoff to make further experiments on animals in which a disturbance of the physiological equilibrium had been produced. As the cutting of the spinal cord caused a decrease of the processes of oxidation in general and of the metabolism of gas especially, and as, besides, the animals suffer greatly by such a traumatic affection, Prof. Prince Tarchanoff undertook a series of experiments in this direction.

The experiments were made on two hundred male frogs of about the same size. All the frogs had their spinal cords severed below the medulla oblongata. In one hundred of these one ccm. of a two-per-cent. solution of *Spermin* (*Spermin-Poehl pro injectione*) was injected into the lymphatic sac in the back of each. The other hundred had a similar quantity of physiological salt-solution injected. This was done because the *Spermin* (*Sperminum-Poehl*) is dissolved in physiological salt-solution.

§ 94. Action of *Sperminum-Poehl* on frogs having spinal cord severed

The results were :

(a) The reflex functions disappeared more slowly in the sperminised than in the other frogs. This was especially noticeable in regard to the tactile reflexes. The sperminised frogs embraced with the front feet things near to them, while in the others the action was but slightly in evidence.

(b) Of the sperminised frogs about 25 per cent. outlived the control frogs.

(c) The length of the time which the sperminised frogs outlived the control animals was in many instances very great. While the control-animals perished in from three to four days (the experiments were made in winter-time, consequently on exhausted frogs), some of the sperminised frogs lived over the ninth day after the separation of the spinal cord.

(d) By repeated injections of a two-per-cent. solution of *Spermin* it was found possible to retard the disappearance of the reflex functions.

These experiments were repeated on three pairs of guinea-pigs and three pairs of white rats. The spinal cord was totally

§ 95. Action of *Sperminum-Poehl* on rats and guinea-pigs having spinal cord severed

cut through at the height of the first sacral vertebra. The operation was, of course, performed with as little loss of blood as possible and under aseptic precautions. Further, in carrying out the experiments the following rule was always observed, that in weak animals and such as had suffered greater loss of blood, the injections of *Spermin* (*Sperminum-Poehl pro injectione*) were employed, while the stronger animals, which were used for the control-experiments, received the physiological salt-solution.

The results were :

On the day after the operation the tactile reflexes appeared in all the animals experimented on. In the control-animals, in consequence of the paralysis of the sphincter-muscles of the bladder and the rectum emissions were of continual occurrence, making the back wet and dirty, while the sperminised animals distinguished themselves by the dryness and cleanness of their backs, thus indicating the absence of paralysis of the sphincter-muscles. At the same time the sperminised animals distinguished themselves by the easier healing and a quicker cicatrization of the wound.

Three of the control-animals died during the fourth and fifth days, while the sperminised animals survived the operation for several months. The injections of *Spermin* consisted in the beginning of two ampullæ in a day and later one of *Sperminum-Poehl pro injectione*. In the control-animals some tonic contractions of the hind feet occurred which were entirely absent from the sperminised animals.

§ 96. Action
of *Sper-*
minum-Poehl
on artificial
epilepsy in
animals

In the guinea-pigs the following interesting observation was also made. In them, as already observed by Brown-Séquard and his followers, on injury to the spinal cord periods of artificial epilepsy occurred with epileptogenic zones of the skin. These were also found in two of the three control guinea-pigs, while in the three sperminised animals no signs of the artificial epilepsy were observable during several months. This fact is highly interesting as it demonstrates the extraordinary tonic action of *Spermin* on the central nervous system.

In the use of his testicle emulsion Brown-Séquard has called attention to its stimulating effect on the emptying of the bladder and on defecation weakened by age or disease. These observations agree entirely with the above-mentioned experiments of Prof. Prince Tarchanoff.

The idea of an increase of vitality (that is, the power of resistance of the nervous elements) caused Prof. Prince Tarchanoff to try Spermin in chloroform-narcosis.

It appears from the observations made with chloroform that the sperminised frogs resisted the paralysing action of the chloroform longer, withstood the narcosis easier, and showed less disturbances of the heart-action than the normal control-frogs. Hence, the former stood larger doses of chloroform than the control-animals. This conclusion applies equally to the case of dogs.

In moderate and large doses *Spermin* produced in frogs retardation and strengthening of the heart-action. In dogs this effect appeared simultaneously, though not constantly, with an increase of the blood-pressure. In most cases the administration of such large doses as 0.4 gm. gave no indication of any influence on the vascular system, even on graphical representation of the effect.

Prof. Prince Tarchanoff also made a series of experiments on the influence of *Sperminum-Poehl* on the development of animals.

We give here only one table of observations on nine young dogs from one litter, which took place on October 25, 1890. On November 6 the experiment commenced. Five of the animals were subjected to the action of *Spermin*, and four to the physiological salt-solution. In size there was one appreciable difference in the dogs. Their weight was first taken on the thirteenth day after the experiments.

§ 97. Action of *Sperminum-Poehl* on the effects of chloroform in animals

§ 98. Influence of *Sperminum-Poehl* on animals' growth

Dogs under the influence of Spermin.					—	Dogs under the influence of physiological Salt-solution.			
I.	II.	III.	IV.	V.		I.	II.	III.	IV.
970	927	825	795	895	November 19	775	750	570	785
1060	1045	865	785	1050	" 24	735	775	570	850
1215	1140	1080	785	1266	" 28	830	945	540	972
1235	1105	1070	760	1365	December 1	842	992	525	1033
1422	1052	1211	778	1555	" 5	936	1162	514	1215
1602	—	1230	—	1773	" 7	1564	1345	died	950
1840	died	1375	died	1795	" 20	died	1322		1057
2062		1517		1955	" 24		1497		1175
2145		1600		2000	" 27		1570		1210
2790		2065		2605	January 3		1980		1590
3275		2350		3302	" 10		2365		1465
3822		2855		3962	" 17		2782		2327
4840		3505		4802	" 25		3612		2932
9691		3960		5582	" 31		3732		3432

In the course of the first month the five dogs subjected to the Spermin-action received three times weekly 0.04 *Spermin* (that is two ccm. of a two-per-cent. solution), and later on the same quantity twice, and subsequently once a week.

The sperminised animals had not only, as the weight demonstrated, grown heavier; they were also larger and more lively than the control-animals. To what this influence of *Sperminum-Poehl* on the growth is to be attributed, Prof. Prince Tarchanoff leaves undecided. Whether the leucocytosis caused by the *Spermin* or the increase of the textural respiration exercises this favouring influence, is an open question.

It should be stated that though only one table of results is given, similar experiments have yielded similar results.

In the same year, 1891, Prof. Prince Tarchanoff made experiments on frogs under the influence of strychnine, with the result in some cases that striking antitetanic effects were exhibited in sperminised animals, while in others these effects were absent. Later experiments of Prof. Prince Tarchanoff have shown that the antitetanic effect was caused by a compound present in the *Spermin*. Further investigations on this substance, which is contained in the testicles, are still pending. It appears to be a compound very much akin to adrenalin. In making his extracts from the adrenal glands, the spleen, and other organs, Dr. Kondratjeff²⁵⁴, found that they had pronounced antitetanic effects in tetanus of bacterial origin; while Prof. Tarchanoff examined them, and found they influenced the tetanus produced by strychnia-poisoning.

In 1896 Prof. Poehl chemically examined the extracts of Dr. Kondratjeff. When subsequently he discovered adrenal and compounds similar to it in the suprarenal glands, the spleen, and other organs, and compared the chemical qualities of Kondratjeff's extracts therewith, it became evident that Dr. Kondratjeff had experimented with compounds similar to adrenal.

Prof. Prince Tarchanoff²⁵⁵ has since demonstrated by direct experiment that adrenal really possesses antitetanic qualities. If one considers that in medicine preparations which are chemically absolutely pure are non-existent, such an occurrence is easily understood, especially in the case of a preparation like *Spermin*, the manufacturing of which offers

such enormous difficulties. In the alkaloids in general use, as, for instance, atropia, quinia, and morphine, the manufacture of which is comparatively easy, and for decades has been technically executed in very large quantities, an absolute purity is *de facto* not obtainable.

In an article published later in 1896, Prof. Prince Tarchanoff very properly remarks: "The exclusion of the antitetanic action, which I previously mentioned, from the physiological qualities of *Spermin* facilitates the explanation of its work in the organism—viz., that of the essential agency of the intraorganic oxidation. Of all the actions that I demonstrated experimentally, only this antitetanic action of *Spermin* could not be explained by its activity as ferment of oxidation. Still, the correctness of this view of the action of *Spermin* is no longer subject to doubt after the publication of the eminent work by Armand Gautier, 'Les toxines microbiennes et animales,' in which this highly gifted author calls *Spermin* the chief weapon with which the organism frees itself from the toxins by oxidation."

As we shall see later, in 1891 the experiments made on animals by Prof. Prince Tarchanoff demonstrated clearly the nature of the action of *Sperminum-Poehl* on the increase of the power of resistance of the organism to exterior injurious influences.

Clinical observations also are agreeable as to this quality of *Spermin*, though the correct explanation of the manifold effects was lacking. After Prof. Poehl had recognised the physiological-chemical significance of *Spermin*, it followed as a natural consequence that he saw in this physiological stimulant one of the means whereby Nature protected our organism against danger from infection, and equally for the maintenance of immunity against other outside influences. In his communication to the Paris Academy of Sciences, in 1892,²⁵⁶ Poehl expressed this view: "If life is a constant fight against death, *Spermin* is for the cell one of the most important means of resistance." In 1887 by urinalyses he convinced himself that most of the infectious diseases go hand in hand with decreased intraorganic oxidation,²⁵⁷ and he recognised that the predisposition to different infectious diseases is to be looked for in the auto-intoxications from decreased textural respiration.

§ 99. Natural
and acquired
immunity

Between natural and acquired immunity a distinction must be made, and as they exist under two different conditions, they will be considered separately. As the biological-chemical qualities of the originators of infection (micro-organisms and ferments) are different, that is to say, as the pathogenic micro-organisms develop their vital activity only under certain chemical conditions (as, for instance, aërobic and anaërobic forms), and as similarly the enzymes practise their functions only under generally fixed conditions (temperature and reaction of the medium), it is naturally to be expected that immunity against the different originators of disease should be based on different biological-chemical moments. In spite of these differences between the conditions of the immunity it is not absolutely necessary that in every infectious disease specific antitoxins must be formed. The latter assumption has been established in the writings of modern investigators, more especially in those of Behring.

§ 100. Power
of resistance
of the
organism and
textural
respiration

Poehl,²⁵⁸ on the contrary, feels justified in assuming that for natural, as well as acquired, immunity certain individual biological-chemical factors from which most of the present prevailing theories of immunity receive an individual explanation. Thus as far back as 1893 he pointed out that the existing condition of the intraorganic oxidation as of the textural respiration, is of the greatest significance as to the power of resistance of the organism against certain diseases.²⁵⁹

As before stated, Poehl has recognised the alkalinity of the blood and the active condition of the *Spermin* depending thereupon as the most essential factors in textural respiration.

§ 101. Leu-
cocyto-
sis and
formation of
spermin

All the factors in the decrease of the alkalinity of the blood—as, for instance, the different auto-intoxications, irritation and exhaustion of the nervous system—decrease the immunity, because textural respiration is decreased. Consequently *Spermin* not only provides the self-protection of the organism, but it also increases the immunity.

Seeing that of the normal nuclein containing textural elements, setting aside certain glandular epithelia, chiefly leucocytes alone (Horbaczewsky²⁶⁰), disintegrate, the formation of *Spermin* will depend mainly upon the quantity of leucocytes that decompose. According to Poehl the essence of the

immunity and immunisation is to be looked for in the leucocytosis which takes place during the normal alkalinity of the blood and the disintegration of leucocytes that follows it.

Leucocytosis is a reaction of the blood against the appearance of foreign substances in it. The chemotactic action of the different products of the bacteria, as well as the bacteria themselves, and even of some indifferent compounds, produces, as is well known, leucocytosis.* The phagocytosis of Metschnikoff, according to Poehl, depends on this chemotactic action, and the result of the fight of the leucocytes with the bacteria, as well as their products, is, according to Poehl, mainly dependent upon the reaction of the medium in which the disintegration of the leucocytes, and relatively the formation of *Spermin*, takes place. In an alkaline medium the leucocytosis will have an immunising significance, as owing to the decomposition on nuclein-containing leucocytes some soluble active *Spermin* is formed which brings the intraorganic oxidation to the normal and so increases the power of the organism to resist noxious influences. The leucocytosis, however, will have no immunising effect during a decreased alkalinity of the blood, because then some inactive, insoluble phosphate of *Spermin* is formed (amorphous or in the form of Charcot-Leyden's crystals).

This theory of Poehl recently received a further explanation. *Spermin*, as the positive katalysator of the processes of oxidation in the organism, is rendered inactive by the presence of acids. Acids play the part of antikatalysators, that is, paralisators, in relation to *Spermin*.

Bredig²⁶¹ emphasises the paralisatory action of acids on the oxydases. It therefore becomes evident that the acids appearing in the textural juices, especially lactic acid, play the part of negative katalysators of textural respiration, that is, they render the *Spermin* inactive.

* In leucocytosis, the quantity as well as the quality of the excitors exercises an essential influence on the character of the chemotaxis. (Pfeiffer first distinguished the positive chemotaxis from the negative, by which is understood the positive or negative power of attraction of certain chemical substances on the leucocytes.) Poehl believes that in this is to be found an explanation of the fact that (for instance) rinna, if used in small quantities, has positive (Cuttler and Bradford, *cf.* Rieder, p. 168) and in large ones negative chemotaxis (Podwyssozki, "General Pathology"—in Russian—1894).

§ 102. Phagocytosis

§ 103. Acidulation of the textural juices decreases immunity

Poehl's investigations on the metabolism have demonstrated that in an organism affected with an infectious disease *Spermin* is rendered inactive and an auto-intoxication results, as appears from the decrease of the intraorganic oxidation, as well as the alkalinity of the blood. Further, the inactivity of the *Spermin* which occurs in these diseases, is frequently demonstrated too by the appearance of Charcot-Leyden crystals in the organism of such patients (Leichtenstern, Neumann, Kunz, Nothnagel). After the introduction of active *Spermin* (*Sperminum-Poehl*) into the organism of such patients, Poehl²⁶² had occasion to point primarily to an increase of the intraorganic oxidation, as well as of the alkalinity of the blood, as may be seen from the following results of the urinalysis :

(a) The coefficient of oxidation (Poehl-Robin) increased as the amount of the intermediary nitrogenous compounds in the urine decreased ;

(b) The proportion of the urea to the ClNa became normal as the amount of the chlorides increased ;

(c) Zerner's coefficient, that is the proportion of the quantity of uric acid to the quantity of phosphoric acid in the form of dinatrium-phosphate, came closer to the normal, as either the quantity of uric acid decreased or that of phosphoric acid contained in the urine in the form of dinatrium-phosphate increased ;

(d) The proportion of the total of the phosphoric acid in the urine to that in the form of dinatrium-phosphate, changed in such a manner that the amount of dinatrium-phosphate in the urine increased. In this proportion Poehl recognises the best expression of the action of *Spermin* on the increase of the alkalinity of the blood. These investigations were made by Poehl on a large number of people suffering from cholera asiatica, phthisis, scurvy, and typhoid fever.

As already stated, acids produce inactivity of *Spermin*, resulting in a decrease of the intraorganic oxidation. Consequently, a suspension of the immunity may follow. Thus Metschnikoff²⁶³ has already stated that the addition of small quantities of lactic acid to a weakened culture of the bacilli which cause the symptomatic carbuncle destroys the immunity in guinea-pigs. In accordance herewith is the fact, established by Charrin and Roger,²⁶⁴ that immunity is also lost by fatigue. This is in perfect consonance with Poehl's²⁶⁵ statements, as fatigue is known to accompany a decrease of textural alkalinity.

Behring²⁶⁶ has already called attention to the fact that the blood-serum of white rats which are almost immune against anthrax has the power of inhibiting the culture of the bacterium anthracis, which he first brought forward in connection with the high alkalinity of this serum. V. Fodor²⁶⁷ showed that the blood of rabbits has stronger bactericide qualities after the injection of an alkali and that consequently the animals are much more immune against the anthrax-virus. V. Fodor, therefore, tested the alkalinity of the blood after the injection of different pathogenic germs and from his experiments on animals reached the following conclusions: "The organism reacts against certain pathogenic infections with a rapid increase of the alkalinity of the blood, which is followed by a larger or smaller decrease of the same. When the infection is fatal, this decrease of the alkalinity is considerable and progressive. When not fatal, the loss is not so great, while the alkalinity rises again and may even exceed the original degree. There is consequently a relation between the effects of certain pathogenic bacteria in the organism and the alkalinity of the blood. If the alkalinity increases after the infection, the animal generally becomes more resistant to the specific bacteria. The degree of alkalinity, as well as the power, with an energetic increase of this alkalinity, of reacting against an infection seems to exercise a remarkable influence on the immunity and the susceptibility of the animals against certain infections."

Further observations which v. Fodor and G. Riegler²⁶⁸ made in common confirm that protective vaccinations increase the alkalinity of the blood. The classical experiments of Senator, Loewy, and Richter have also shown that Spermin increases the alkalinity of the blood and operates towards immunisation. We shall deal with this matter later on.

Buchner's theory of immunity (formation of bactericide, dissolved substances in the organism—so-called alexins) is sufficiently explained by the formation of Spermin and similar substances produced by the leucocytosis and the subsequent disintegration of leucocytes. According to Koch, Ehrlich, Behring, Roux, Buchner, Brieger, Wassermann, etc., immunity is produced by the formation of an antitoxin. The existence of the antitoxins is of itself not impossible. The question, however, remains open whether in each case a specific antitoxin must necessarily be formed. Buchner²⁶⁹ has already arrived at the following conclusion: The action of the antitoxins does not consist of a direct destruction of the specific poisons of the bacteria on contact with them; it occurs only within the organism and through its mediation. Roux expresses himself against the specific character of the antitoxins, and considers them as products of the living cells exclusively.

The theories of Buchner, as well as of Roux, are perfectly consonant with Poehl's Spermin theory. At a meeting of

§ 104. Anti-
toxin and
spermin

naturalists in Vienna, Wassermann²⁷⁰ said: "A very great number of individuals who never had diphtheria show in their serum some pronounced qualifications for the destruction of the diphtheria-poison. The frequency of the occurrence of such serum increases with increasing age."

When we consider this fact, it becomes evident that the immunising principle is not to be looked for in an occasionally appearing antitoxin. We must expect to find it normally, as an always present constituent of the blood.

Artificial immunity and its artificial increase by successive intoxications or infections is explained by Behring as owing to the artificially produced leucocytosis coexisting with an increase in the alkalinity of the blood.

As far back as 1892 Prof. S. S. Botkin,²⁷¹ on the occasion of some hematological investigations during injections of tuberculin (*Deutsche med. Wochenschr.* 1892, No. 15) and his observations in croupous pneumonia and tetanus (*Bevl. Klin. Wochenschr.* 1892, No. 19), expressed the opinion that the products of the disintegration of leucocytes cause a destruction of poison.

G. v. Bunge²⁷² expresses the supposition that it depends especially upon leucocytes to render the noxious substances harmless. A more precise theory of the destruction of the nitrogenous products of the retrogressive metamorphosis, that is, the leucomaines, is offered by Armand Gautier²⁷³ in his extremely interesting investigations on the chemistry of the living cell; he admits as a necessary requirement the existence of an oxidising ferment and locates the destruction of the leucomaines in the outer sheath of the cell.

Three English *savants*, namely, Hankin, Kanthack, and Hardy,²⁷⁴ have more closely defined the action of leucocytes in the inflammatory reaction. In the opinion of these authorities, the eosinophile leucocytes play the most important part in the phagocytosis, by leaving the blood-vessels and migrating directly to the infected place. In Hankin's opinion even Buchner's alexins are nothing more than a product of the eosinophile cells. The connection of eosinophile cells with *Spermin* and equally with Charcot-Leyden crystals, has been emphasised by Prof. Poehl on many occasions. The connection between eosinophile cells and Charcot-Leyden crystals (phosphate of Spermin) has been established first by v. Leyden,²⁷⁵ and later on several occasions by different observers.

Finally, it may be mentioned that *Spermin* has a direct influence on the biological-chemical qualities of pathogenic microbes; Poehl²⁷⁶ has demonstrated experimentally that the bacteria of cholera asiatica, when cultivated in a Spermin-containing medium, lose the faculty of giving the indol-reaction (cholera-red, according to Poehl²⁷⁷). This means the loss of their toxicity (experiments of Brieger, Wassermann, and Kitasato).

§ 105. Innoxious leucocytosis and formation of spermin as protective means against infection

When recapitulating the foregoing facts, we come to the following conclusions concerning the action of *Spermin* in the symptoms of immunity and immunisation. The appearance of the pathogenic microbes and enzymes in the organism is attended with leucocytosis as a reaction. When the leucocytosis

which is produced in this manner takes place under favourable conditions, that is, in an alkaline menstruum, by the decomposition of the nuclein and the formation of soluble active *Spermin* the textural respiration is increased, and the intra-organic oxidation is brought to the normal, while the power of resistance of the organism against infection is strengthened. When, however, the leucocytosis takes place under unfavourable conditions, that is with decreased alkalinity of the blood, as a product of disintegration of the nuclein (of the leucocytes), the insoluble, inactive *Spermin* is formed. Consequently the accumulation of the xanthin-bases, which did not proceed to perfect oxidation, and of leucomaines will still increase the already existing auto-intoxication, as is the case, for instance, in the cachectic and premortal leucocytosis. Poehl therefore expresses belief in two kinds of leucocytosis, namely a benign and a malign one. By direct introduction of active *Spermin* (*Sperminum-Poehl*) into the organism some favourable effects of the leucocytosis can be obtained, without being exposed to the danger of producing a malign leucocytosis. Further, *Spermin* by its action on the biological-chemical qualities of some pathogenic microbes may directly diminish the danger of the infection and intoxication.

So far went Prof. Poehl's communications to the Imperial Academy of Sciences at St. Petersburg in 1894.

Several months later Prof. Senator on the occasion of the discussion of a paper read by Poehl, entitled, "Concerning the Physiological Chemistry of the Textural Juice Therapy generally, and the *Spermin* Therapy especially,"²⁷⁸ communicated his experiences with *Sperminum-Poehl*. As Prof. Senator touches here on the experiments for immunisation, we will quote his words as given in the records of the meeting.

Prof. Senator²⁷⁹ says: "In the discussion which took place here some time ago on the textural juice therapy, I mentioned that I had made experiments with *Spermin* in several diseases, especially in diabetes and tabes. The result was that, while the tabetic patient felt subjectively better, objectively no improvement could be shown. It seemed to me more fitting first to ascertain whether *Spermin* has any effect at all on the metabolism, before I experimented on diseases with conditions so complex, especially changes in the

metabolism of so complicated and partially unknown characters I had taken no account of the expositions of Mr. Poehl, because they were almost altogether of a speculative nature only. Something, of course, can be said in favour of his theories. They are, however, far from being proved, and even if, *e.g.*, everything that he assumes concerning alkalinity in diseases were correct, one may still ask if there are not other conditions present in the diseases, which may interfere with the action of the *Spermin*. Shortly, it seemed to me necessary to determine by exact experiments whether *Spermin* has any influence on the metabolism, and I induced my assistant, Dr. P. Richter, to make some experiments with *Spermin*. He afterwards continued these independently in other directions together with Dr. Ad. Loewy. These experiments are not yet completed, however. Still, they have already had some remarkable results. First and foremost, it has demonstrated that *Spermin* has a pronounced influence on the blood, especially on the leucocytes. After the introduction of *Spermin* a great diminution in the number of leucocytes occurs, caused by leucolysis, and this is soon followed by hyperleucocytosis. That the decrease of the leucocytes is really caused by the destruction of some of them and not by an abnormal distribution in the capillaries, is to be concluded from another fact which becomes clear upon the introduction of *Spermin*, that is, a considerable increase in the alkalinity of the blood. This begins even before the hyperleucocytosis, in the stage of the decrease of the leucocytes in the sample of blood. It would be difficult to account for this in any other way than by leucolysis. The method by which the alkalinity of the blood was determined, is that originated by Mr. Ad. Loewy. It is probably the only reliable one so far known. Into other results I will here not enter, because the experiments in other directions are not yet numerous enough. *Spermin*, then, has really an effect in the direction which Mr. Poehl has intimated. Whether this effect, however, can be used therapeutically, is yet to be discovered. As before stated, we do not know whether, besides the decrease of the alkalinity, there are not in diseases other changes which interfere with the action of *Spermin*. In any case it seems to me improper to make experiments with it just from the standpoint of our

views of to-day, according to which the leucocytes play an important part in many diseases, especially of an infectious character."

The *Semaine médicale* (*cf.* *Semaine médicale*, 1895, No. 28) gives in its account of this discussion another passage from the communication made by Prof. Senator: "The results which (at the examination of the effects of *Sperminum-Poehl*) I obtained in conjunction with Dr. Richter, are very important. The action of *Spermin* on the blood is established beyond doubt. When *Spermin* was being employed we observe in the beginning a strong leucocytosis, followed by hyperleucocytosis, and at the same time an increase in the alkalinity of the blood which is beyond doubt. These facts speak in favour of the theory of Prof. Poehl, even if one cannot agree with all the conclusions which the author of the theory draws from it. In any case *Spermin* is a very active substance whose results, at least partly, occur in the manner stated by Prof. Poehl."

"Drs. Richter and Loewy have with *Spermin* cured a number of animals that had been infected with pneumonia, to which they would doubtless have succumbed had not they been treated with *Spermin*."

Soon afterwards G. Epifanoff²⁸⁰ published the results of the investigations he had made in the clinics of Prof. L. Popoff, entitling it: "On the Influence of Hypodermic Injections of *Sperminum-Poehl* on the Morphology of the Blood in Healthy and Sick Persons."

The influence of the injections of *Spermin* on the amount of the leucocytes in the blood seems to depend on the stage of disease. If the injection coincides with the commencing crisis or is made immediately before it, a hyperleucocytosis occurs without a consequent leucocytosis. If, however, the injection is made at an earlier stage of the disease, at the development of the leucocytosis, no decrease of the amount of the leucocytes is found. A very large increase in their number takes place.

Thereupon Loewy and Richter²⁸¹ published their investigations, under the title: "On the Influence of Fever and Leucocytosis on the Course of Infectious Diseases." They report in the following manner as to their experiments with *Sperminum-Poehl*:

§ 106. *Sperminum-Poehl* subdues infection with pneumococcus

"The therapeutic effect in the pneumococcus-infection is striking. If the pneumococci were injected after a leucocytosis had been produced by this remedy (*Sperminum-Poehl*) and maintained by repeated injections, we always succeeded in curing the animals which had received three or four times the fatal dose. It was also striking that in the majority of cases, if the experiment was arranged in this manner, no or only very little rise of temperature could be observed as a sign of general infection and the animals presented only slight symptoms of disease. Much less was the therapeutic effect when such leucocytosis-producing means were introduced twenty-four hours or more after the infection with pneumococci had taken place. Here with the same doses as in the former experiments occasionally an even considerable prolongation of life, but not a final cure was obtained."

In a later communication Loewy and Richter²⁸⁸ give some further observations on the action of *Sperminum-Poehl* and other leucocytosis-promoting means in artificial infections. They say: "We had therefore to look for some means by which the desired effect could be obtained without any concomitant symptoms threatening the life, and we found them in *Sperminum-Poehl* and the nuclein. The former in hypodermic, as well as intravenous, application invariably proved absolutely harmless, while the latter, at least in intravenous injection, was not always found quite harmless."

As the observations of Loewy and Richter just mentioned have not only a theoretical interest by affording us an insight into the biology of leucocytes, but also discover some important points favourable to the Spermin-theory, we will quote a few passages in the authors' own words:

"To what extent the changes in the number of the leucocytes might influence the course of the infection, was investigated from the following points of view:

"(a) Investigation was made to discover what the effect was, when *Sperminum-Poehl* and nuclein were administered only some time after the injection of the different kinds of bacteria, and the hyper-leucocytosis was produced subsequent to the infection.

"(b) When both were injected at the same time.

(c) When *Sperminum-Poehl* or nuclein was injected first and the animal was exposed to the bacterial infection later on.

It may be especially mentioned that for every experiment-animal or every series of experiment-animals, a control-animal, or a series of small animals was selected, all being injected on the same day with similar doses of the same culture. Mistakes are only to be avoided in this way, as from the varying degree in the virulence of the cultures they may easily be made.

As to the experiments in chicken-cholera, we succeeded only in a few cases in obtaining a decided effect from our leucocytosis-promoting means, and this only when just about a single lethal dose of the requisite culture had been used. In such cases we occasionally obtained a complete cure. This, however, only occurred when the effect of the bacterial infection appeared subsequent to our having produced hyperleucocytosis. The first pathological symptoms, consisting in rises of temperature, appeared in our control-animals from three to four hours after the hypodermic injection. At about the same time on intravenous injection of *Spermin* hyperleucocytosis appeared and lasted from twenty to twenty-four hours. Continued injections increased and prolonged this hyperleucocytosis. The following table shows how by adaptation of these varying times a desired effect could be obtained.

§ 107. *Sperminum-Poehl* subdues chicken-cholera

I. Control-animal receives :

June 22, 1896, at 12 noon, 0.01 of a chicken-cholera bouillon-culture (that is the fatal dose).

4.30 P.M. 40.4°, 6.30 P.M. 41.3°, 8.30 P.M. 41.2°

June 23, in the morning the animal was found dead.

II. Experiment-animal receives :

June 22, 11.5 A.M. 1.5 gm. *Sperminum-Poehl** intra-venously.

„ 11.10 A.M. 0.01 Chicken-cholera bouillon intra-venously.

„ 12.10 P.M. 40° This little rise of temperature is caused by the *Spermin*, as we repeatedly observed.

* In all the experiments of Prof. Senator, Ad. Loewy, and Richter as *Sperminum-Poehl* the two-per-cent. solution of *Sperminum-Poehl pro injectione*

June 22	4 P.M.	40°	
"	6 P.M.	41.2°	1 grm. <i>Sperminum-Poehl</i> intravenously (ear-vein).
"	8.30 P.M.	40.1°	
June 23	9 A.M.	39.3°	Animal very weak, without other symptoms of disease.
"	11.30 A.M.	39.3°	1.40 P.M. 39.5°
"	4 P.M.	39.5°	6 P.M. 39.7°
June 24	11 A.M.	39.9°	Animal very weak. Does not eat.
"	12.30 P.M.	39.7°	4 P.M. 39.6°
"	5.30 P.M.	39.8°	
June 25	12.30 P.M.	39.2°	Animal lively ; eats.
"	2 P.M.	39.6°	4.30 P.M. 39.4°
"	6.45 P.M.	39.4	

The animal remained alive.

When, however, the single fatal dose was only slightly exceeded, there may be some short prolongations of life, but no further cures were possible. In this regard the following experiment, which was made on the same day and with the same culture, as the previous one, but with a rather larger dose, is very interesting.

II. (a) Control-animal.

June 22, 11.45 A.M.	0.015	Chicken-cholera broth-culture hypodermically.
"	1 P.M.	39.3° 4 P.M. 39.9°
"	6.30 P.M.	40.6° 8 P.M. 40.9°

June 23, in the morning the animal was found dead.

(b) Experiment-animal.

June 22, 11.30 A.M.		2 grm. <i>Sperminum-Poehl</i> intravenously.
"	11.45 A.M.	0.015 Chicken-cholera broth hypodermically.
"	12.30 P.M.	39.9° 4.30 P.M. 39.4°
"	6 P.M.	40° 1 gr. <i>Sperminum-Poehl</i> two per cent. intravenously (ear-vein).
June 23	9 A.M.	40.6° 1 P.M. 38.1°
"	4.30 P.M.	37.1° 6 P.M. dead.

in ampullis has been used ; when the *Essentia Spermini-Poehl* was used, it is so stated.

Thus, only a slightly later appearance of the first symptoms of the disease and a prolongation of the life for from twelve to fifteen hours was all that resulted. The knowledge we obtained on the occasion of our investigations into the influence of an increase of the temperature of the animal body on the chicken-cholera infection, viz., that the effect obtained is by no means proportionate to the amount of the infecting dose, hereby received strong corroboration. Life was prolonged but for a few hours, no matter whether the dose employed amounted to a thousand times or only twice the lethal dose.

At the same time, it seems very remarkable that by an artificial production of hyperleucocytosis, if but in a few solitary instances, a cure could be obtained. The salutary influence of the artificial increase of the temperature, which we have shown was, however, powerless here.

We now come to the communication of the results by Prof. Loewy and Richter in pneumonia-infection. The results vary owing to the temporary arrangement for the experiments :

§ 108. Further experiments with Sperminum-Poehl in pneumonia infection

(1) The results were worst, when the hyperleucocytosis-producing means were employed subsequent to the pneumonia-infection having taken place. A pronounced effect, however, was also evident here. It appeared on the one hand in the changed course of the infection in the experiment animals—in so far as the increase of the temperature, which is its visible expression occurred later—and, on the other hand, in the protracted course of the disease. Anyhow, it invariably ended in death, although occasionally considerable periods elapsed before the fatal time arrived.

The following will show the nature of the experiment :

(a) Control-animal.

March 22, 1895. A white rabbit never before used. Temp., 39.5°, receives hypodermically :

March 22.—12.40 P.M., 0.00005 of a very virulent pneumonia broth-culture ; 4 P.M., 39.5° ; 6 P.M., 39.7°.

March 23.—10 A.M., 40.1° ; 12 (noon), 40.4° ; 2 P.M., 40.1° ; 4 P.M., 40.8° ; 6 P.M., 39°.

March 23.—10 A.M., 40.1° ; 12 (noon), 40.4° ; 2 P.M., 40.1° ; 4 P.M., 40.8° ; 6 P.M., 39°.

March 24.—Found dead.

(b) Experiment-animal (Experiment No. 36).

A white rabbit never before used. Temp., 39.3°.

March 22.—12.45 P.M., 0.00005 pneumonia broth-culture, hypodermically

injected. 4 P.M., 39.2°; 6 P.M., 39.3°; 1.5 grm. of sperminum-Poehl two-per-cent. intravenously injected.

March 23.—10 A.M., 39°; 11 A.M., 38.5°; 2 P.M., 39°; 4 P.M., 39.5°; 6 P.M., 39.5°.

March 24.—9 A.M., 39.9°; 11 A.M., 40.5°; 12.30 P.M., 40.5°; 3 P.M., 41.5°; 4.30 P.M., 41.8°.

March 25.—8 A.M., 39°; oedematous swelling of the snout: animal very weak; 10 A.M., 38.2°; 12.30 P.M., dead.

The life of the experiment-animal lasted seventy-two hours as against forty hours in the control-animal. An interesting phenomenon is the delay of the rise of temperature in the treated animal. Here it commences only forty-four hours after the inoculation, while in the control-animal it began after twenty hours. From the beginning of the infection, which shows itself by the rise of temperature, however, there is no noticeable difference in the manner of the course in the two cases, nor in the time in which death ensues.

(2) Considerably more favourable, however, were the results obtained by Loewy and Richter, when the means producing hyperleucocytosis were employed simultaneously with or even before the infecting agency. Thus, in both cases, hyperleucocytosis already existed, when the bacterial infection appeared; at least when *Spermin* was given intravenously and the pneumococci hypodermically. It was then possible to obtain a complete cure (even after the quadruple lethal dose), or at least some very considerable prolongations of life. Examples of both may be seen in the following:

(1) (a) Control-animal receives on March 16, 1895, 0.0001 pneumonia-broth (= four times the fatal dose).

March 16.—10.45 A.M., 39°; inoculation. 12.30 P.M., 39.5°; 4 P.M., 39.5°; 5 P.M., 39.6°; 6.30 P.M., 39.9°.

March 17.—8.30 A.M., 41.1°; 11 A.M., 40.8°; 2 P.M., 41°; 4 P.M., 41.1°; 6 P.M., 40.7°.

March 18.—Found dead early in the morning.

(b) Experiment-animal (No. 33) received on March 16, at 11.15 A.M., 0.0001 pneumonia-broth hypodermically and at the same time 1.5 gr. *Sperminum-Poehl* intravenously.

March 16.—12.30 P.M., 39.8°; 3 P.M., 39°; 5 P.M., 39.7°; 26,200 leucocytes; 6.30 P.M., 39.8°.

March 17.—8 A.M., 39.3°; 24,800 leucocytes, 11 A.M., 39.1°; 12 (noon), 39.4°; 1 grm. sperminum-Poehl two-per-cent. intravenously; 4.30 P.M., 39.9°; 7 P.M., 39.6°.

March 18.—10 A.M., 39.3°; animal without symptoms of disease; 1 grm. *Sperminum-Poehl* injected. 1.20 P.M., 39.5°, 20,200 leucocytes; 4 P.M., 39.4°; 6.15 P.M., 39.5°.

March 19.—10 A.M., 39.2°, 18,000 leucocytes; 6 P.M., 39.4°.

March 20.—10 A.M., 39.3°; 6 P.M., 39.4°.

March 21.—9 A.M., 39.3°; 5 P.M., 39.4°.

March 22.—9 A.M., 39.1°.

March 23.—12 (mid-day), 39.1°.

The animal remained alive.

(2) (a) Control-animal received on February 22, 0.0002 pneumonia-broth (lethal dose = 0.00005).

February 22.—11.20 A.M., 39°; inoculation at 4 P.M., 39.4°; 6 P.M., 39.8°.

February 23.—9 A.M., 39.9°; 12.20 P.M., 40.6°; 2.20 P.M., 40.8°; 5 P.M., 40.5°; 6.30 A.M., 40.6°.

February 24.—10 A.M., 39.1°, animal very weak; 11.30 A.M., 38°; 12 (noon) dead.

(b) Experiment-animal (No. 17) receives on February 22, at 11 A.M., 1 grm. Sperminum-Poehl two-per-cent. intravenously, and at 1 P.M. 0.0002 pneumonia-broth. Leucocytes, 19,400.

February 22.—3 P.M., 39.1°; 4.30 P.M., 39.3°; 6 P.M., 39.6; 23,600 leucocytes.

February 23.—8.40 A.M., 39.8°; 10.30 A.M., 39.8°, 16,000 leucocytes; 1 grm. Sperminum-Poehl two-per-cent. intravenously.

February 23.—1.30 P.M., 39.9°; 4 P.M., 40°; 6 P.M., 40°, 22,400 leucocytes.

February 24.—8 A.M., 40.1°; 11.30 A.M., 41.3°; 1 P.M., 41.1°.

February 25.—9.30 A.M., 40.5°, has diarrhoea, is lively and eats; 10.40 A.M., 40.5°; 1 P.M., 40.6°; 4 P.M., 40.9°; 6.30 P.M., 41.1°.

February 26.—10.30 A.M., 41°, 15,800 leucocytes; 1.30 P.M., 40.6°; 4 P.M., 40.5°; 6 P.M., 40.7°.

February 27.—10 A.M., 41°; 1 P.M., 40.2°; 4 P.M., 40.8°; 6 P.M., 41.1°.

February 28.—9.30 A.M., 40.1°; 12 (noon) 40.5°; 4 P.M., 40.7°; 6 P.M., 40.5°.

March 1.—Animal much emaciated, has severe diarrhoea, does not eat; 8 A.M., 39.3°; 10 A.M., 38.5°; 1 P.M., 37.5°; 4 P.M., 37.4°; 6 P.M., 38°.

March 2.—Animal found dead.

Thus, in a number of animals of which the above given experiment (1) is an example, no pathological symptoms whatever developed. The animals appeared perfectly normal, and there was no indication of the grave infection which had taken place. In some, however—experiment (b) is an example—it led to high rises of temperature which lasted for days, the animals finally succumbing under symptoms of inanition. In such cases, however, a complete recovery was occasionally obtained. The following experiment will serve as example:

(a) Control-animal received on October 23, 1895, at 11.30 A.M., 0.03 pneumonia-broth (= twice the fatal dose).

October 23.—2 P.M., 38.7°; 8 P.M., 40.1°.

October 24.—8 A.M., 40.8°; 12 (noon) 40.7°. 4 P.M., 39.9°. 7 P.M., 39.1°; very weak.

October 25.—Found dead in the morning.

(b) Experiment-animal (No. 43) received on October 23, at 10.50 A.M., 0.15 nuclein intravenously injected and at the same time 0.03 pneumonia-broth hypodermically.

October 23.—12.30 P.M., 38.9°, 14,800 leucocytes; 1.20 P.M., 39.1°, 28,200 leucocytes; 4.20 P.M., 39.5°.

October 24.—9 A.M., 39.8° 31,800 leucocytes; 11 A.M., 39.9°, 0.1 nuclein intravenously; 2 P.M., 40.0°, 28,200 leucocytes; 5 P.M., 40.6°.

October 25.—9 A.M., 41.2°, 15,000 leucocytes; 2 P.M., 41.3°, eats and is lively.

October 26.—9 A.M., 40.9°, 14,300 leucocytes; 1 P.M., 40.7°; 5 P.M., 40.3°.

October 27.—9 A.M., 40.3°; 5 P.M., 39.9°.

October 28.—9 A.M., 39.5°, 11,200 leucocytes; 5 P.M., 39.8°.

October 29.—9 A.M., 39.3°; 5 P.M., 38.7°.

Animal remains alive.

§ 109. *Sperminum-Poehl*
in diphtheria
poison

Finally, we come to our experiments made with the virus of diphtheria (Aronson). Here, too, we have succeeded in obtaining some cures, but only isolated cases and after administering the exact fatal dose.

The following experiment will illustrate this:

(a) Control-animal received on November 22, at 11.50 A.M., 0.05 diphtheria virus intravenously (ear-vein).

November 22.—4 P.M., 39.2°; 5.30 P.M., 39.3°; 7 P.M., 40.5°.

November 23.—9.40 A.M., 38°; 11.45 A.M., 37°; 2 P.M., dead.

(b) Experiment-animal (No. 50) received on November 23, at 12 (noon), 2 grm. *Sperminum-Poehl* two-per-cent. intravenously and five minutes later 0.05 diphtheria virus intravenously.

November 23.—3.30 P.M., 39.2°; 5 P.M., 39.5°, 17,200 leucocytes.

November 24.—10 A.M., 39.5°; 12 (noon) 39.5°, 14,800 leucocytes; 2 grm. *Sperminum-Poehl* two per cent. hypodermically; 4 P.M., 40.2°, 16,600 leucocytes; 6.30 P.M., 39.7°.

November 25.—10 A.M., 39.3°; 12 M., 39.7°, 1 grm. *Sperminum-Poehl* hypodermically; 4 P.M., 39.7°.

November 26.—9.30 A.M., 39.2°; 11 A.M., 39.5°; 12.30 P.M., 39.5°; 4 P.M., 39.4°; 6 P.M. 39.4°.

November 27.—10.30 A.M., 39.2°; 1.30 P.M., 39.3°; 6 P.M., 39.2°.

November 28.—9 A.M., 39°.

The animal survived.

That here, however, we have to deal with but a momentary delay in the action of the virus and not in the least with a vaccinate protection, is shown by the following experiment which was made on the same animal three days later.

The same animal received another 0.05 diphtheria-virus intravenously on November 30.

December 1.—12 (noon), 39.3°; 4 P.M., 39.5; 6.30 P.M., 40°.

December 2.—8.30 P.M., 40.5°; 11.20 A.M., 40.5°; 2 P.M., 40.1°; 5 P.M., 37.6°.

December 3.—The animal was found dead in the morning.

Prof. Loewy and Richter continue the description of their experiments as follows: "In a series of other experiments no cures were obtained, but only a lengthening of life varying from twenty-four to seventy-two hours. It was quite immaterial whether the diphtheria virus was given, as in the above reported cases, intravenously or hypodermically. Still, in opposition to the method of procedure observed by others, we preferred the intravenous administration because after the hypodermic injection of the diphtheria-virus the course became very irregular. Often no rise of temperature occurred, and the beginning of the infection was therefore not recognisable. The effects of the infection appeared later in the animals previously treated, and the course in their case was different from that in the control-animals as it was nearly always accompanied by very high temperatures (occasionally over 41°).

The latter point is not altogether without interest, when attention is called to the fact that the control-animals after the fatal doses had little or no fever, and that their temperature even fell away considerably, while after doses of the virus amounting to about one half or a quarter of the fatal one, occasional large increases in the temperature of the body were observed.

Although the results obtained with the diphtheria virus are considerably poorer than those with the pneumococcus infection, they are theoretically not without significance, because for the first time it has been demonstrated that against a pure action of toxin the artificially produced hyperleucocytosis has also to some extent a favourable influence. That this is much more limited is easy to understand; for, during infection with living bacteria they only form their poisons later and in small quantities, while the finished diphtheria-virus operates immediately and in full concentration.

When we summarise our results, an evident influence of the hyperleucocytosis is unmistakable, which, of course, varies with the different inciters of the infection. As we have seen, it is much more pronounced in the pneumococcus infection than in that with chicken-cholera.

When reviewing the results of the investigations of Loewy and Richter, we must not forget that they were not made for the purpose of testing the effects of *Sperminum-Poehl*. These authors, in the first place, intended to inquire into the part played by leucocytosis in infectious diseases, and they selected *Sperminum-Poehl* simply because this means was the only one which either on hypodermic injection or on intravenous introduction was perfectly harmless.

If Loewy and Richter in the experiments No. 36 and others had not limited themselves to one injection, the experiment-animals would in all probability have remained alive.

Loewy and Richter, as Prof. Poehl points out, convinced themselves that the original theory of Metschnikoff as to the phagocytic activity of the leucocytes, which by the incorporation of the bacteria into the cell makes the former harmless, is no longer tenable. The protective action has much more of a chemical nature and originates in certain products of the cell.

In 1892 Prof. S. S. Botkin²⁸⁴ expressed the opinion that the products of disintegration of the leucocytes brought about destruction of the poisons. According to Buchner and Hahn, this is caused by certain products of secretion of the leucocytes which they name "alexins." The alexins, however, have not yet been chemically isolated and we know therefore nothing of their chemical nature.

Hahn²⁸⁵ has shown that in the dog the blood, in the stage of hyperleucocytosis, has a stronger bactericidal action. He has also demonstrated by a small, but convincing, number of experiments that in men also the bactericidal power of the human blood increases with the increase of the hyperleucocytosis.

Loewy and Richter show that in the so-called hyperleucocytosis an increase in the alkalinity of the blood takes place, and they assume that the lessening of the leucocytes is caused by a disintegration of leucocytes.

Caro and Strauss²⁸⁶ have made experiments showing that changes in

§ 110. Protective action in leucocytosis is caused by chemical products of the cell

the alkalinity of the blood cannot always be demonstrated after the use of substances which affect the operation of the leucocytes. Experiments have not been made, however, with *Spermin*.

Loewit²⁸⁷ reports that in the first stages of artificially produced infectious diseases in guinea-pigs and rabbits, he found a considerable rise in the alkalinity of the blood: "In the experiments reported the increase in the alkalinity of the blood appears as a forerunner of the subsequent decrease which is in accordance with the views expressed by Loewy and Richter. Here the idea certainly seems to suggest itself that in the increase in the alkalinity we have a protective measure or counter-reaction of the diseased organism against the cause of the disease and its effects." Later on, Loewit, in an experimental study,²⁸⁸ enters into the question of the relations between the amount of the leucocytes and the degree of the alkalinity. He endeavoured to produce in the blood a change in the leucocytes without a previous infection or intoxication, which on its own account may affect the alkalinity, and for this purpose he selected the ligature of the aorta. This produced a decrease of the leucocytes. The latter, however, as Loewit has already demonstrated, is not based on a destruction of the white blood-corpuscles—a leucolysis—but on their diminished afflux from the central into the surrounding parts—a "leucopenia." Now it appears in the experiments of Loewit that in those cases in which the number of the leucocytes decreases considerably the alkalinity is proportionately lessened. Hence, as Loewy and Richter emphasise, a connection is experimentally demonstrated between the number of the leucocytes and the degree of alkalinity. It might, therefore, appear on superficial observation as though the results of Loewit were opposed to those of Loewy and Richter. These authors, after injecting certain substances in hyperleucocytosis, found not a decrease but an increase in the alkalinity. As Loewit himself declares, however, the question in these experiments is not a diminished afflux of leucocytes, but an increased disintegration of them. He considers his results not as contrary to, but necessary supplements of, those of Loewy and Richter.

That there exists a connection between the alkalinity of the blood and the number of the leucocytes appears to be established by the investigations of Loewit and Loewy and Richter. It only remains, then, to be shown that hyperleucocytosis in these latter experiments has been produced by a disintegration of leucocytes.

Loewit further confirms the relation between the alkalinity of the blood and its protective power. Hence it appears that, so long as the number of leucocytes in the blood is still somewhere about a thousand, its bactericidal strength is practically unchanged. Only when it falls below this already minimum value, is its strength impaired or entirely suspended.

A much-debated statement made by Virchow more than fifty years ago has been amply confirmed. He said: "I claim for the white blood-corpuscles a place in pathology," and

Prof. Minkowski²⁸⁹ very properly adds: "and for therapeutics."

As regards the articles of Profs. Loewy and Richter and Dr. Jacob ("Zeitschrift fuer Klinische Medicin," 1896) on the influence of the different degrees and stages of the alterations of the leucocytes during the course of the infection in the animal body we would refer to the original and to the discussion of this subject by Prof. Poehl in his "Spermin Theory," pp. 107-117.

As to the origin of the pretended protective substances of the blood, the opinion has often been expressed, and even quite recently (Büchner, Hahn, Jacob and others), that we have to deal with secretory products of the white blood-corpuscles.

§ 111. Influence of Sperminum-Poehl on the alkalinity of the blood

The results obtained as to the increase in the alkalinity have led Loewy and Richter to express the opinion that it is the disintegration of the leucocytes to which these protective substances owe their origin. Direct proof of the disintegration of white blood-corpuscles is furnished by the microscopical observations of Loewy and S. S. Botkin. Buerger, Kitasato and Wassermann also contend that this is the case.

It remains only to be established whether chemical evidence for such a disintegration can be given, primarily by the direct demonstration of the presence of substances in the blood whose relation to the leucocytes is established.

Loewy and Richter satisfied themselves that during the changes in the amount of leucocytes which they produced, some bodies are to be found in the blood which either wholly or in part have the character of albumoses.

The presence of these bodies can only be positively shown, however, under certain specified conditions. After injections of nuclein and Sperminum-Poehl they are to be found in the stage of the primary hyperleucocytosis; after pilocarpin, however, they are not found at this stage. After the administration of nuclein the experiment invariably succeeds in from four to fifteen minutes after the injection. On one occasion, however, a weak reaction was obtained only after thirty minutes (Experiment 4).²⁹⁰ On the other hand, in two

experiments no albumoses were discovered even as long as twenty-eight and thirty-eight minutes respectively after the injection (Experiments 9 and 6 b).²⁹¹ Counting the blood-cells showed that here, after the hyperleucocytosis stage was ended, the number of the cells had again risen slightly above what was usual.

In the experiments with *Sperminum-Poehl* the albumoses were to be found six minutes after the injection.

Further, with one exception, in all the cases that were examined for it, albumoses could be demonstrated in the course of the hyperleucocytosis, especially in the declining stage. Let us first consider the experiments with pilocarpine. Among them²⁹² Experiment 13 is the exception mentioned, in which even forty-five minutes after the introduction no albumoses could be detected. The action of the pilocarpine was in this case, however, but insignificant, no regular hyperleucocytosis appeared and the subsequent increase in the number of the leucocytes did not exceed 13,000. The albumose reaction, however, was clear in experiments Nos. 11, 12, 14, 15,²⁹³ especially in the two last, in which after a large increase (up to 20,800) the number of the blood-corpuscles was speedily again on the decrease.

Colourless cells contain albumose-like substances that can be extracted from them by chemical means. The investigations which led to this result were made with colourless cells of different kinds, as, for instance, pus- and lymphatic-cells, and the results obtained, according to Loewy and Richter, may, without hesitation, be applied to the colourless cells circulating in the blood. Furthermore, they are of opinion that, in the event of an extended decomposition of colourless cells taking place in the animal organism, while its products pass over into the blood, the result should be their excretion in the form of albumoses with consequent albumosuria. Therefore, this latter occurs in empyema pleuræ, in purulent bronchitis, in purulent diseases of the bones, as well as in purulent decomposition of lymphatic glands and in re-absorption of cellular infiltrations, as, *e.g.*, in erysipelas, in the re-absorption of the cellular pneumonic exudation, etc.

The albumosuria is in these cases considered as a direct sign of the disintegration of colourless cells and of the passing over of their constituents into the blood (Hofmeister, Stadelmann, Senator and others).

The significance of the statement that in the experiments with nuclein and *Sperminum-Poehl* albumoses are found during the course of the hyperleucosis as well as the hyperleucocytosis, while in those with pilocarpine they are found only in the latter stage, will be discussed later.

The first question that arises here is : To what causes shall we refer the chemical changes which we find in the blood ?

It is certain that it is a modification of albuminous material, and of such albuminous material as belongs to the blood. It must not be assumed that the constituents of the plasma are the home of the albumoses, nor is there any indication that the injection of the substances used by Loewy and

Richter would exercise such an influence as to change the character of the molecule of the nitrogenous, organic constituents of the blood-fluid.

With the cellular elements of the blood it is different. We admittedly have no knowledge of a connection between a change in the red blood-cells and the appearance of modified albuminous substances in the blood. Some experiments which Loewy and Richter undertook in this direction testify against such a connection. So much the more certain, however, are the relations between the colourless cells and the formation of albumoses.

It must, however, be stated that so far albumoses have never been demonstrated as existing in the blood in its normal state, though it is frequently found in leuchæmic blood. More reasonably, therefore, may they be traced to the leucocytes, as their increased disintegration in leuchæmia seems now to be fully established both chemically and morphologically.

Considering all these facts, together with the statement that in the stage of a declining hyperleucocytosis, as has been demonstrated by experiments, an increased disintegration of leucocytes takes place, the conclusion arrived at by Loewy and Richter is amply justified, and the appearance of albumoses in the blood which they observed in the experimental leucocytosis may also be connected with this increased destruction of the leucocytes.

Loewy and Richter, however, in their experiments with nuclein and spermin found albumoses not only in the stage in which the number of the leucocytes is resuming the normal, but also in the early stage preceding the hyperleucocytosis, which shows a large diminution in the number of leucocytes below that which is usual. The fact that both stages in which a decrease in the number of the leucocytes occurs have the same effect on the chemical constitution of the blood supports the opinion already expressed by them, viz., that in both we have to deal with similar processes, so that if in the one case an increased disintegration of leucocytes has been demonstrated, a like result should also be assumed in the other.

For the primary hyperleucocytic stage, however, this increased disintegration is denied by some authors. They assert that, as already mentioned, there is only an accumulation in certain capillary districts of the leucocytes which have been circulating in the blood. These authors, however, call attention to the fact that so far as the former are concerned, and relying on the results of their experiments, an accumulation of the white blood-cells has been shown, while an increase of the disintegration cannot be denied.

In a former article Loewy and Richter expressed their belief in the disintegration of leucocytes, on the ground of the change in the alkalinity of the blood. They could not believe that the latter could be produced simply by a change in distribution. Nor could they in this way account for the development of albumoses. The presence of albumoses in hyperleucocytosis is clearly an indication of a disintegration, because it agrees with the same occurrence during the course of the hyperleucocytosis in which a disintegration of colourless cells in different ways may be considered as established beyond question.

A peculiar fact respecting the stage of the hyperleucocytosis is held as a result of the experiments with pilocarpine—albumoses are not found there. As we have already stated, Loewy and Richter have also shown that the conditions in the alkalinity of the blood under similar circumstances do not experience any changes so far as an increase are concerned. The values of the alkalinity of the blood which they furnish from their experiments

point in isolated cases to a decrease in the alkalinity of the blood after injections of pilocarpine. Poehl is of opinion that the decrease in the alkalinity of the blood after the injections of pilocarpine precludes the formation of *Spermin* in the blood during the disintegration of the leucocytes, and considers that herein lies the explanation of the statements above-mentioned.

Prof. Minkowski,²⁹⁵ on the occasion of his lecture on leuchæmia and leucocytes before the Seventeenth Congress for Internal Medicine, expresses his firm belief that in leucocytosis we have a valuable aid in our therapeutic work. This confidence is based on the one hand on the fact that here the question is of processes which are in the closest relation with the protective efforts and the healing processes in the organism, and on the other hand that we are in a position to exercise such influence on these processes as we desire.

Minkowski speaks here of organic extracts; the appropriate experiments with *Sperminum-Poehl* made by Profs. Prince Tarchanoff, Loewy, Richter, Popoff, Epifanoff, etc., seem, however, to be unknown to him, as he mentions the use of *Sperminum-Poehl* only in leuchæmia. This is not less remarkable, however, than the statement made by Prof. Klemperer,²⁹⁶ before the Association of Naturalists at Kassel in 1903, viz., that from the literature on the subject no positive therapeutic results from the use of *Sperminum-Poehl* were known to him (*sic*!). In this discussion of the leucocytosis by Prof. Minkowski, we miss altogether consideration of the question of the alkalinity of the blood, the significance of which so far as the matter of immunity is concerned, as is evident from his former articles, is unquestionably known to Prof. Minkowski.

We believe that the case mentioned by Minkowski (that of Knehnau and Weiss) of a quick development of lymphatic leuchæmia after an injection of pilocarpine (on the occasion of a pseudo-leuchæmia) arose from a decreased alkalinity of the blood.

§ 112. Leucolysis in decreased alkalinity of the blood

In Poehl's opinion, as already mentioned, the difference between the effects of the leucolysis after *Sperminum-Poehl* and after pilocarpine is to be explained by the fact that in the leucolysis after *Sperminum-Poehl* the intraorganic oxidation, and hence also the alkalinity of the blood, are increased; while in the leucolysis after pilocarpine the intraorganic oxidation is speedily diminished. Poehl accounts for the appearance of sweat after pilocarpine partly by the fact that the accumulation of the intermediary products of the metabolism is greater, and the organism endeavours to protect itself against this auto-intoxication by the elimination of leucomaines through the sweat-glands. The appearance of sweat may in all probability be explained as owing directly to a burdening of the nervous tissue with accumulated products of metabolism and the consequent irritation of the vasomotors.

We fully agree with the opinion of Argutinsky,²⁹⁷ and particularly with that of Neumeister,²⁹⁸ that the sweat under certain circumstances plays

an essential part in the elimination of the end-products of the metabolism. As Argutinsky has shown the existence in the sweat, besides the normal constituents of the urine, of kreatinin (Tichborne²⁹⁹), uric acid (Kast³⁰⁰), some aromatic oxy-acids, phenol-ether, and skatosylether-sulphuric acid, we may safely assume that the sweat is one of the means by which the organism under certain circumstances protects itself against the auto-intoxications.

It only remains to add a few words on the effects of *Sperminum-Poehl* on the secretion of sweat. § 113. Decrease of the secretion of sweat by Sperminum-Poehl

Prof. W. Stange observed that in patients in whom sweat appeared after the administration of phenacetin * there was no such result on the employment of *Sperminum-Poehl*. Repeated experiments have but tended to strengthen the results of Prof. Stange's observations.

This observation of Prof. Stange has since been repeatedly confirmed. In the next chapter we give the results of observations made by Podkopajeff, Cohn, Bukojemsky, Pant-schenko, and Bartoschewitsck, who, after treatment with *Sperminum-Poehl*, have observed a diminution in the night-sweats of consumptives.

The above-mentioned differences between the effects of *Sperminum-Poehl* and those of pilocarpine on the leucocytosis entitle Poehl to the assumption, in consideration of the action of *Sperminum-Poehl* on the secretion of the sweat, that the increased sweat-secretion in certain cases is to be accounted for by an increased leucolysis in a decreased alkalinity of the juices.

We have satisfied ourselves that the increase of textural respiration accompanies the increase in the alkalinity of the blood. In the formation of carbonic acid—which is contemporary with the oxidation of organic substances, especially of the organic acids causing acidulation of the tissues—the organism possesses a safety-valve to prevent the alkalinity of § 114. Normal alkalinity of the textural juices naturally causes immunity

* The action of the fever-remedies from the group of the aromatic compounds is explained by Poehl, as well as others, as attributable to their capability of forming substitution- and addition-products with the leucomaines, and thereby influencing the auto-intoxication (*cf.* Poehl, *Verhandl. d. Kongr. f. innere Medizin.* 1896, Wiesbaden, pp. 84-86; *Ueber den Wert der arzneilichen Antipyretica*). These aromatic products of substitution and addition are sometimes eliminated with the sweat. Kast (*loc. cit.*) has shown that with their secretions the sweat-glands excrete some aromatic compounds, though under normal conditions the sweat-glands do not perform such elimination (Senator: *Virchow's Archiv.* 1877, p. 1882).

the juices from ever becoming too high. The increased formation of carbonic acid is productive of a rise in the "partial pressure" in the textural juices. On the other hand, a normal alkalinity of the textural juices is one of the most essential conditions for the maintenance, that is, the restoration of the natural immunity.

The significance, therefore, of the physiological Spermin for natural immunity clear from all that has been said, while the Spermin therapy, as a means of counteracting the auto-intoxications and other forces predisposing to infection, is as clearly theoretically founded. Practical experience with *Sperminum-Poehl* at the sick-bed repeatedly confirms these theories.

§ 115. The counter-action to the deleterious action of plasma-poisons on the lighting bacteria by *Sperminum-Poehl*

The action of *Sperminum-Poehl* on the diminished textural respiration has been demonstrated by Prof. Prince Tarchanoff³⁰¹ by several extremely interesting experiments. As result of his investigations on the phosphorescent bacteria of the sea he satisfied himself that the luminosity is connected with the function of breathing. It became evident that the plasma-poisons—chloroform, ether, alcohol, and hydrocyanic acid—cause this brightness to cease. The addition of *Sperminum-Poehl* to a culture, the luminosity of which has ceased owing to the action of one of the plasma-poisons, causes the shining to begin again in a short time. For instance, after a slight addition of a two-per-cent. solution of hydrocyanic acid (*vide* experiments of Prof. Prince Tarchanoff with Richard v. Poehl) to a broth-culture of phosphorescent bacteria the brightness soon disappears. Upon the addition of *Sperminum-Poehl*, however, it speedily became again luminous.

§ 116. Influence of *Sperminum-Poehl* on the biological-chemical processes of cholera bacilli

Another proof as to the action of *Sperminum-Poehl* on the biological-chemical processes in low organisms is to be seen in the experiments which Prof. A. v. Poehl made on cholera bacilli. During the investigations which Poehl³⁰² made in 1886 for the examination of the biological-chemical qualities of these bacilli he recognised that by their vital activity they cause in the surrounding medium some phenomena of reduction which he considered as connected with the formation of ptomaines. At the same time he satisfied himself that the vital activity of the cholera bacilli causes the formation of a substance from which, on treatment with muriatic acid, a red pigment originates. This pigment he mixed with amylalcohol and determined its characteristic absorption-spectrum. He

repeated this experiment many times, and all the investigators have corroborated the fact he records (viz., Dunham,³⁰³ Bujwid,³⁰⁴ Brieger,³⁰⁵ E. Salkowski,³⁰⁶ Jadassohn,³⁰⁷ Zaeslein,³⁰⁸ Petri³⁰⁹).

This so-called "cholera-red reaction" was, with others, employed for the purpose of demonstrating Koch's comma bacilli.

The red pigment is an indol-derivate.

With the intention of studying the influence of *Sperminum-Poehl* on the biological-chemical qualities of the cholera bacilli, Poehl made the following experiment: To some freshly made nutrient-jelly he added *Spermin* (to ten parts of the nutrient-jelly one part of the ten-per-cent. solution of *Sperminum-Poehl*). The mixture was distributed in test-tubes, sterilised and inoculated with cholera asiatica. Further a portion of the original nutrient-jelly was inoculated with the same cholera culture. A few days later, when Poehl added muriatic acid to the cholera cultures that had not been treated with *Spermin*, the mass turned red. Amyl alcohol added to the mixture, and shaken, absorbed the red pigment. The solution showed the characteristic absorption-spectrum described by Poehl. In the cultures which developed in the nutrient-jelly to which *Spermin* had been added, the presence of the pigment could not be demonstrated even in the presence of muriatic acid and amyl alcohol, although, save for the addition of *Spermin*, the cultures had been similarly treated. The addition of *Spermin* has no retarding influence on the development of the cultures.

The non-appearance of the cholera-red reaction in the cultures of cholera asiatica in the presence of *Spermin* clearly indicates a change in the metabolism of these bacilli in a *Spermin*-containing medium. From this the conclusion can be drawn that in the presence of *Spermin* the cholera bacilli do not produce reduction-symptoms which are peculiar to cholera asiatica. It therefore follows, concludes Poehl, that *Spermin* interferes with the formation of ptomaines.

We have, then, in this experiment strong proof that the presence of *Spermin* causes the disappearance of the reduction processes, and has an oxidising action.*

* As is known,⁷ the extremely interesting experiments of Brieger, Kitasato, and Wassermann have shown that cholera cultures lose their toxic

This experiment tells strongly in favour of the idea that Spermin has an influence also on the vital functions of a micro-organism which otherwise has a reducing action on its medium, in such a manner as is in entire consonance with the oxidising effect of Spermin on more highly developed organisms.

§ 117. Action
of spermin
rendering
toxins non-
toxic

Recently Prof. Prince Tarchanoff and Dr. Alf. v. Poehl have, by a series of experiments on animals, continued their observations on the influence of *Sperminum-Poehl* on the processes of oxidation. Until now there were no direct experiments to hand that made it possible to prove that a toxic leucomaine (which acts no small part in auto-intoxications) in the organism is rendered non-toxic by the action of *Sperminum-Poehl*.

Neurin is one of the most toxic leucomaines, and, as appears from the most recent investigations, forms itself in the organism *intra vitam* under normal as well as pathological conditions.

This highly toxic compound has been found in normal blood by F. Marino-Zuco and U. Dutto,³¹⁰ as well as by F. Marino-Zuco and C. C. Martini³¹¹; while Marino-Zuco³¹² has demonstrated the existence of neurin in the urine in cases of Addison's disease.

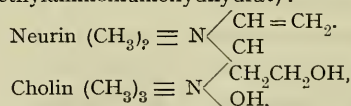
Later, F. W. Mott and W. D. Halliburton³¹³ have shown that neurin was found in the blood of a patient affected with beri-beri.

Cholin, which is nearly allied to neurin, has been obtained by Liebreich,³¹⁴ as a splitting-product of protagon, and by Diakonow³¹⁵ as a splitting-product of lecithin.

Gulewitsch³¹⁶ has shown that neurin is found already existing in the normal brain. According to Armand Gautier³¹⁷ neurin is contained in the brains and the nervous substance simultaneously with cholin.

Mott and Halliburton³¹⁸ have demonstrated cholin in the cerebro-spinal fluid of patients suffering from general paralysis and atrophy of the brain.

According to published statements made by A. Gautier,³¹⁹ neurin (trimethylvenylammoniumhydroxyd) is twenty times more poisonous than cholin (trimethyloxaethylammoniumoxyhydrat):

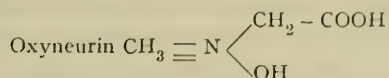


Loen and P. Ehrlich³²⁰ think the greater toxic qualities of neurin are attributable to the double union in the vinyl group ($\text{CH} = \text{CH}_2$).

By oxidation, as already demonstrated by Liebreich, neurin is changed

qualities in an extract of the thymus gland. This result probably arises from the fact demonstrated by Poehl, viz., that the thymus gland contains a large amount of Spermin.

to the perfectly non-toxic oxyneurin (betain) and the double union referred to is solved.



Frogs (*rana temporaria*) proved especially suitable for these experiments with neurin and cholin. These experiments of Prof. Prince v. Tarchanoff and Dr. Alfr. v. Poehl are so striking that, performed in the following manner, they can be used for demonstrations in a lecture.

Take a very dilute solution of neurin (twenty drops of a twenty-five per cent. solution of neurin to fifty gm. of normal salt solution). Of this diluted solution inject 0.3 or 0.4 ccm. into the thigh of the frog. In this way the experiment-animal receives at once from 0.0015 to 0.002 of neurin. After fifteen to twenty minutes some very pronounced toxic symptoms appear: first paresis, then paralysis of the hind-extremities with simultaneous contraction of the front feet and analgesia of the whole skin, and finally retardation and cessation of the heart-beat.

The paralysis of the hind-extremities is in neurin- and curare-poisoning caused by the numbing action of these poisons on the terminals of the motoric nerves, though neither the N. ischiadicus nor the muscles lose their respective irritability and contractibility. By direct irritation with the faradic current the muscles of the hind-legs can be made to contract; though this cannot be done through the N. ischiadicus. That the nerve-trunk itself is not paralysed by the neurin is demonstrated by the known form of the experiment made in curare-poisoning. A ligature is placed around the upper part of the thigh, excluding the N. ischiadicus. In this way the entrance of the blood poisoned by neurin is prevented. Then, in neurin- as well as curare-poisoning, this extremity keeps its irritability and mobility, and reacts with movements on every irritation of the sensitive surface of the skin, while all the other members of the body remain quite immovable. It is therefore evident that neither the nerve-trunks nor the muscles, but only the terminals of the motoric nerves in the muscles, are paralysed by the neurin. A very essential difference between neurin- and curare-poisoning, so far as concerns the nervous-muscular system, exists in the as yet unaccounted-for fact that the fore-legs of animals poisoned

with neurin remain in a condition of contraction. In the male frogs this contraction appears in the form of an embrace, while in the female the upper extremities are pressed against the body in a quite characteristic manner. These latter symptoms are not observed in curare-poisoning in which all the extremities are in a relaxed, paralytic condition.

Having described the course of neurin-poisoning in frogs, we now pass to the experiments touching the action of *Sperminum-Poehl* on animals poisoned with neurin. For the purposes of these experiments a pair of frogs of the same sex and weight, and of about the same liveliness, must always be selected.

To the experiment-frog give two ccm. *Sperminum-Poehl*, to the other (the control-animal) two ccm. of normal salt solution. Five minutes later inject into the lymphatic sac of the thigh of both animals the above-mentioned toxic dose of neurin.

In all these experiments, if only they are carefully executed, that is, if the injections are made into the lymphatic sac only and not into the circulation or the muscular tissue, the same result is always obtained.

In the sperminised frogs the symptoms of neurin-poisoning rarely appear at all, and even where they do appear it is only in very weak form and always later than in the control-animals.

This important fact, which has been demonstrated by Prof. Prince Tarchanoff, together with Dr. Alfred v. Poehl, is explained by the assumption that *Spermin* as a positive katalysator increases the processes of oxidation in the organism and by oxidation changes the neurin to an innocuous compound (oxyneurin?).

As is known, atropin was considered as the only antidote in neurin-poisoning, because it raises the retardation and the stagnation of the heart. It influences, however, the symptoms only of the neurin-poisoning, while the neurin remains unchanged and yet another poison is added. *Spermin*, however, protects the body against poisoning with neurin, because by increased combustion it destroys the poison itself.

After all that has been said it was interesting to study the influence of *Sperminum-Poehl* on poisoning with curare.

All the experiments of Prof. Prince Tarchanoff, however,

gave but negative results in this respect. In curare-poisoning *Spermin* produced neither a retardation nor a weakening of the symptoms of the intoxication. This circumstance is probably accounted for by the fact that curare is chemically a very stable poison, which in the organism is not easily amenable to oxidation and, as is known, is excreted by the urine undecomposed. It is therefore easy to understand that the increase of the processes of oxidation by the *Spermin* cannot exercise any influence on curare-poisoning.

In cholin-poisoning, too, *Sperminum-Poehl* acts counter to the poison, as is shown by the following experiment of Prof. Prince v. Tarchanoff.

To frogs 0.5 ccm. of a ten-per-cent. solution of cholin was injected into the lymphatic sac of the back. Those frogs in whom two to four ccm. of a two-per-cent. solution of *Spermin* had been at first injected, recovered from the poisoning, while those to whom an equal quantity of normal salt solution had been given instead of the *Spermin*, showed all the symptoms of cholin-poisoning. The paralytic condition of the muscular tissue with simultaneous analgesia—symptoms which are mainly caused by the influence of cholin on the central nervous system—disappeared in the sperminised frogs sooner than in the control-animals. It is evident, therefore, that in neurin we have also to deal with a destruction of the poison by oxidation.

As to the toxic effects of cholin and neurin, they differ not only quantitatively, but qualitatively. It is assumed that neurin and cholin operate similarly; with this difference, however, that neurin operates some twenty times or more stronger than cholin. As a matter of fact, however, this can hardly be the case, as the course of a cholin-poisoning indicates chiefly an affection of the central nervous system, while neurin-poisoning approaches more nearly to curare-poisoning, in which the motoric terminals of the nerves in the muscles are affected.

Still, be that as it may, the above-mentioned difference in the effects of neurin and cholin have no essential significance as to the question in which we are interested, because the counteracting effects of *Sperminum-Poehl* are not based on the removal of the symptoms of the poisoning, but on the destruction of the particular poison by oxidation.

The typical counteraction of *Sperminum-Poehl* referred to—as we see from the following—is also seen at the sick bed. We would refer here to a case in which the course of the disease represented either a cholin- or a neurin-poisoning.

On July 24, 1901, into the hospital of the administration of the palace of Tsarskoe Sselo (near St. Petersburg) was brought the peasant woman M.P. From July 21 she had been in a cataleptic condition which lasted until August 12, a period of twenty-two days. For thirteen days she was treated uselessly with injections of strychnia and camphor; then by order of the chief surgeon of the hospital, the court physician Dr. Dantschitsch, and the ordinator Dr. W. Jaroschewsky, from August 3 daily four injections of *Sperminum-Poehl* were given. Some thorough analyses of the urine in the case were made by Prof. Poehl. After the patient received twenty-five injections of *Spermin*, on August 10 she commenced to perform some movements, and woke up fully on August 12. It appeared that the patient recollected everything that had happened around her in those twenty-two days; she could even repeat the smallest details of the conversations carried on near her.

The urinalyses showed in this case an essential deviation from the usual course of the action of *Spermin* on the urine. The coefficient of oxidation was first but very slightly increased, as may be seen from the following statements: August 2 = 87.35; August 4 = 87.37; August 7 = 89.81; August 9 = 87.74; August 10 = 87.05. Very marked, however, was the influence of the *Sperminum-Poehl* on Zuelzer's co-efficient which steadily rose from August 3 to 10 from 15 to 19.5. On August 2, before the injection of *Spermin*, it was 15; on August 4—after it—15.5; on August 7, 20.5; on the 9th it was 20.7, and on the 10th, 19.5. The urea-chloride of sodium coefficient, which was very low, quickly commenced to rise under the influence of the *Sperminum-Poehl*. On August 2 it was 8.93; on the 4th, 13.8; on the 7th, 27.1; on the 9th it was 26.8, and on the 10th, 25.1.

In this case we have apparently to deal in the first place with a destruction of poison in the organism and comparatively less with the removal of the products of metabolism.

That the processes of oxidation are simultaneously

increased, appears from Eichwald-Bouveret's coefficient. The foregoing statements are made for the purpose of showing that the therapeutic effects of *Sperminum-Poehl* are not always visible in the increase of the coefficient of oxidation alone, but to enable us to arrive at a definite conclusion, we have always to consider at the same time all the factors, namely, the coefficients of urine.

The case of katatony just referred to is very instructive, because it can evidently be explained as arising from an auto-intoxication of the organism with a poison which is in its effects similar to neurin. Here as well as there the most important symptom was general muscular weakness, which went on as far as complete paralysis accompanied by full consciousness with preservation of all the mental faculties. In both cases *Sperminum-Poehl* showed its therapeutic action.

Consequently it is safe to assume that the pathological symptoms, which are similar to those of curare-poisoning, are not caused by a compound similar to curare, but by a neurin-poison.

As evidence for what we have here said we cite a disease which is known on the island of Ceylon, on the coasts of Malabar and in India, under the name of beriberi. To the symptoms of this disease belong in the first place numbness of the limbs and great loss of power.

During these spells, which resemble the symptoms of neurin-poisoning, Mott and Halliburton found, in the blood of patients suffering therefrom, such large quantities of neurin that they were able to determine the identification and exact nature of this compound.

We know that in the vital activity of some micro-organisms neurin is formed out of lecithin. Lacerda found in hogs suffering with a disease similar to beriberi a course of the disease similar to neurin-poisoning, namely, great loss of power, numbness of the limbs, paralysis of the hind-legs (without paralysis of the front-legs), etc. A micro-organism from the group of the askomycetes, which was recognised by him as the cause of the disease, produces on inoculation in animals a poisoning like that of neurin.

With the above-mentioned observations of Gulewitsch, Gautier, Mott, Halliburton as basis we consider it right to assume that the accumulation of neurin and cholin

originating in the body (which was found as well as others in the central nervous system in cases of general paralysis and atrophy of the brain) must play an important part in the ætiology of different nervous disturbances.

Neurin-intoxications not only take place in cases of katatony, but clearly in other nervous affections as well.

Marino-Zuco and Dutto³²² consider Addison's disease, because of the presence of neurin in the urine, as a neurin auto-intoxication ; and Ed. Boinet³²³ and O. Polimanti³²⁴ express themselves in a similar sense.

Mott and Halliburton³²⁵ arrive at the conclusion that the weakened circulation of the blood together with severe fainting spells and fatty degeneration of the heart, which are so often observable in cases of general paralysis, find explanation in neurin- and cholin-intoxications. According to the observations of Beattie Ne'sbitt³²⁶ neurin-intoxications may also occur from the bowels, as he was able to confirm by direct experiments on animals.

Finally, we might refer also to the observations of C. della Torre who investigated the influence of artificial neurin-intoxication on the metabolism in herbivores and reached similar conclusions as did Poehl in the cataleptic woman. In the first place della Torre points out that the diminution of the chlorides is very pronounced during the period of poisoning.

When we place all these facts and clinical observations together, it is easily understood that the employment of *Sperminum-Poehl*, as a katalysator of oxidation, has often given good results in a large number of nervous affections which are caused by auto-intoxication from the accumulation of neurin, cholin, etc.

We have here to deal with an actually rational treatment of an intoxication and not with the ancient method of counter-poisons which only treats the symptoms by the action of another poison, without destroying the original.

The doctrine of counter-poisons is still defended by such eminent pharmacologists as Prof. Kobert³²⁸ but to-day it is no longer therapeutically tenable for all cases, as Profs. Alb. Robin and Bardet³²⁹ and Prof. Kionka³³⁰ point out. On the doctrine of counter-poisons Prof. Robin expresses himself as follows : " le temps est passé des contrepoisons et des anti-

dotes dont l'action merveilleuse tenait plus du roman que de la réalité ; la doctrine des antagonistes doit être considérée comme surannée, et le médecin qui veut rendre de réels services à son malade en cas d'empoisonnement, doit voir les choses d'une façon beaucoup plus rationnelle et plus élevée qu'autrefois."

The object of Organotherapy is in part to replace the former counter-poisons by innocuous organotherapeutic remedies which either eliminate the poisons or, as in this case, change so poisonous a compound as neurin to the absolutely harmless oxyneurin, in imitation of an experiment already made *in vitro* by Prof. Leibreich.

Under the direction of Prof. Kobert a dissertation has recently been delivered by Dr. A. F. Kakowski³³¹ in which is demonstrated the fact that *Sperminum-Poehl* exercises a very pronounced tonic action on the heart and removes intoxications, as is the case with digitoxin. Prof. Kobert is therefore not at all opposed to the doctrine of the removal of the poison ; rather may we greet him as a follower.

CHAPTER VI

CLINICAL OBSERVATIONS ON THE THERAPEUTIC EFFECTS OF SPERMINUM-POEHL

§ 118. Arrangement
of the clinical
material

IT has been clearly shown in previous chapters that *Sperminum-Poehl*, by its katalytic action, restores the lessened processes of oxidation in the organism to the normal. Hence favourable therapeutic effects have been observed in very varying diseases in which auto-intoxications from decreased textural respiration were present. We subjoin a list of the diseases arranged, as by Poehl in his book, "The Physiological-chemical Foundations of the Spermin Theory with Clinical Material for the Therapeutic Employment of Sperminum-Poehl" (1898).

I. Conditions of Inanition.—This group comprises observations on the therapeutic employment of *Sperminum-Poehl* in :

- (1) Anæmia,
- (2) Tuberculosis,
- (3) Typhoid fever,
- (4) Marasmus senilis,
- (5) Miscarriages,
- (6) Rickets,
- (7) Skin diseases.

II. Anomalies of the Metabolism.

- (1) Uric acid diathesis (arthritis deformans, rheumatism, endarteritis obliterans),
- (2) Scurvy,
- (3) Diabetes mellitus.

III. Diseases of the Nervous System.

- (1) Functional neuroses (neurasthenia, hysteria, epilepsy, chorea, katatony, etc.).
- (2) Organic lesions of the central and peripheric nervous system (tabes dorsalis, paralysis, neuritis, etc.).

IV. Diseases of the Eye.

Atrophy of the optic nerves, asthenopia, nystagmus, etc.

V. Diseases of the Heart, the Lungs and the Kidneys.

VI. Intoxications.

- (1) Intoxication with chloroform and carbon oxide, alcoholism.
- (2) Specific intoxications: syphilis, erysipelas, cholera asiatica.

As may be seen, these groups often comprise forms of disease which clinically are very far apart. This is accounted for by the fact that the classification is based not on the clinical complex of symptoms, but on the sphere and mode of the action of Spermin, which often coincide in very different clinical forms.

For instance, all the diseases of Group I. are characterised by decrease of the intraorganic oxidation. As for anæmia, it has been demonstrated that therein we have always to deal with a decrease of the processes of oxidation (large decrease of the coefficient of oxidation and increase of the toxicity of the urine), as well as a decrease in the alkalinity of the blood.

Before going further into the observations of the different authors, we feel it incumbent on us to settle a very important question, viz., to what extent the material answers the required purpose, or, in other words, to what extent the respective observations from a scientific, clinical point of view meet the varying requirements. Further, in the compilation of the clinical material, the exact observations made in medical clinics have been used, as well as some more or less thorough histories of cases from the private practice of physicians, and finally some short notices of practitioners who have communicated their personal impressions of the results obtained rather than particular histories of cases. The multiplicity of the material as to the clinical scientific value must, of course, also be taken into consideration.

In addition those forms of disease which are characterised by an irregular course (as, *e.g.*, neurasthenia, hysteria, etc.), were taken into consideration. In such cases, of course, one is forced to consider the influence of accessory forces, which might readily lead to the wrong conclusion, "*post hoc ergo propter hoc.*"

It will be readily conceded, too, that no small value is to be attached to the fact that while the different observers acted in absolute independence one of another, they yet reached almost identical results in their observations. And these observations have not been made in a particular practice or place, but in the most different localities, not only of Russia, but of the whole world.

In the monograph of Prof. v. Poehl we find a large quantity of clinical material with the reports of two hundred and thirty observations. In the arrangement of our material we shall follow that of Prof. v. Poehl in his monograph. We shall, however, consider only the most important observations. Those who take more particular interest in similar observations are referred to the monograph of Prof. D. A. v. Poehl.

I. Conditions of Inanition.

(1) Sperminum-Poehl in Anæmia.

OBSERVATIONS OF DR. L. FINKELSTEIN.³³² ANÆMIA.

§ 119. Clinical observations on the therapeutic effects of Sperminum-Poehl in anæmia

Miss M. M., 28 years old, suffered with pronounced anæmia. Despite the customary methods of treatment, the condition of the patient became visibly worse. Finally, the case became absolutely desperate. To the usual symptoms of anæmia were added a series of nervous symptoms. Urinalyses were made three times, and on each occasion Robin-Poehl's co-efficient of oxidation was found very much decreased.

After the first injection of *Sperminum-Poehl*, the patient was sensibly improved, as is evidenced by the record in her day-book. During the further treatment therewith the favourable effects became more and more apparent: the nervous symptoms decreased considerably, and within a month the weight of the body increased five pounds. Even after discontinuation of the Spermin treatment for two months the patient felt comparatively well. After two further months of treatment with *Spermin* the condition of the patient was highly satisfactory, and remained so for a year, although the injections had again been discontinued. Repeated analyses of the urine during the injections showed that the proportion of the urea-nitrogen to the total nitrogen of the urine was materially increased, this indicating an increased intensity of the processes of oxidation in the organism.

Comparatively good results were obtained by Dr. L. Finkelstein in other similar cases, after the exclusive treatment with spermin.

OBSERVATIONS OF DR. A. PODKOPAJEFF.³³³ ANÆMIA.

Dr. A. Podkopajeff describes two cases of chloro-anæmia in which he obtained pronounced improvement by treatment with *Sperminum-Poehl*. In these cases in addition to *Spermin*, iron in the shape of Liq. ferri albuminati was also administered. Further walking exercise in the open air was urgently recommended. In both cases the general condition of the patients improved considerably. "By the use of iron alone," remarks Dr. A. Podkopajeff. "I never obtained good results so quickly or so satisfactorily."

OBSERVATION OF DR. W. PANTSCHENKO.³³⁴ ANÆMIA.

Dr. W. Pantschenko observed a case in which the general condition of his lady patient with pronounced symptoms of anæmia and disorder of the nervous system was much improved after eighty-eight injections, extending over a period of twenty-four days. Besides *Sperminum-Poehl*, Dr. Pantschenko gave Borshom (Caucasus) mineral water to his patient.

The treatment with *Sperminum-Poehl* commenced on June 23. The urinalysis which, unfortunately, was not made before the beginning of the treatment, but only after four injections, on June 25, showed the following: Quantity in the morning, 170 ccm.; the urine, cloudy, acid; specific gravity (at 15° C.), 1022. The amount of indican was increased; abnormal pigments were absent, as well as albumen, pepton and sugar. Urea on 1000 = 31.32. The proportion between the total nitrogen of the urine and the urea-nitrogen was 100 : 90.6 (unfortunately the proportion before the injections is not known, as no analysis had been taken). The sediments consisted of mucus and contained leucocytes, crystals of uric acid, pavement epithelia, and saccharomycetes. After thirty-five injections the urinalysis showed on July 3: Morning quantity, 184 ccm.; the urine cloudy, acid; specific gravity, 1020; less indican than before; abnormal pigments, albumen, pepton and sugar absent. Urea, 25.1 to 1000. The proportion between the total nitrogen of the urine to the nitrogen of the urea was 100 : 86.9 (?). In the sediments mucus, leucocytes, cylindroids and pavement epithelia were found. After eighty-six injections and ten tub-baths from the Eugenia spring (temp. 29°), the urinalysis showed on July 14: Morning quantity, 330 ccm.; the urine was slightly hazy; reaction weakly acid; specific gravity, 1.010; traces of pepton (?); urea, 10.69 to 1000. The proportion of the total nitrogen of the urine to the nitrogen of the urea was 100 : 88. Leucomaines, 0.25 per cent., leucocytes, pavement epithelia.

OBSERVATIONS OF DR. G. v. HIRSCH,³³⁵ PHYSICIAN EXTRAORDINARY
TO HIS MAJESTY THE CZAR. ANÆMIA.

One of his lady patients, who suffered with pronounced anæmia, was treated twice. The first time the patient received the known pills of ferr. sulph. with kali carbon (pilulæ blandi). After about six weeks the patient had almost recovered. After a year, however, her general condition became quite desperate. Then, beside the above-mentioned pills twice a day, twenty drops of *Essentia-Spermini-Poehl* were prescribed in Vichy water. This combined treatment produced an effect of which Dr. G. v. Hirsch says the following: "I must admit that I have rarely seen such a favourable effect of therapeutic measures in any chronic pathological condition as I have noted in this case; for even in the course of three weeks such a change has taken place in the patient as neither she nor I had expected." The improvement in this case was lasting. Two years later Dr. Hirsch convinced himself personally of the perfectly good health of his patient.

In another case Dr. Hirsch stated that on the exclusive use of iron no striking improvement in the condition of the patient occurred, while in the same case after the use of pills of iron first a subjectively better feeling, and later a decidedly visible and lasting improvement took place.

OBSERVATION OF DR. JULIUS URSZINYI.³³⁶ ANÆMIA.

The above observations of Dr. G. v. Hirsch induced Dr. Julius Urszinyi to try *Sperminum-Poehl* in a case of anæmia perniciosa gravis. In his patient

who with an extremely small amount of hæmoglobin was extremely cachectic and short of breath, he found even after the first dose of *Sperminum-Poehl* a surprising improvement in the general condition, as well as complete restoration of the capability to work. Although a complete recovery was hardly to be expected on account of the great atrophy of the mucous membrane of the bowels, the influence of the *Sperminum-Poehl* on the processes of oxidation in the organism was distinctly evident.

OBSERVATIONS OF DR. WICHERT.³³⁷ ANÆMIA.

In spite of the continued use of different (organic as well as inorganic) preparations of iron, which Dr. Wichert employed on his patients, the disease could not be stopped. The excessive anæmia with spells of severe headache went on. The urinalysis showed a decrease of the processes of oxidation (coefficient Robin-Poehl = 100 : 89.64; Zerner's coefficient = 0.79; Zuelzer's = 100 : 22.0) and a diminished alkalinity of the blood (urine coefficient = 100 : 34.1). Beside the injections of Spermin Dr. Wichert prescribed for his patient a predominantly vegetable diet and Vichy water. Thanks to this treatment, the strength of the body increased and the headaches ceased. At the same time Dr. Wichert observed an increase in the energy of the processes of oxidation (coefficient Robin-Poehl = 90.48; Zerner's coefficient = 0.50; Zuelzer's coefficient = 100 : 15.8) and a return of the alkalinity of the blood to the normal (urine coefficient = 100 : 51.1).

§ 120. Explanation of therapeutic action of Sperminum-Poehl in anæmia

It is evident from the results of the urinalyses that in all forms of chronic anæmia we have in the first place to deal with a diminution of the processes of oxidation in the tissues.

(a) Robin-Poehl's coefficient of oxidation is considerably lowered. This is caused by an increase of the intermediary products of metabolism, as has been demonstrated by Scherer, Kossel, Salkowski, Arm. Gautier, Alb. Robin, Pouchet, v. Jaksch, Koerner, Salomon, Nencki, Sieber, Stadthagen, R. Schmidt.

(b) The proportion of the chlorides of the urine to the urea is below the normal.

Our idea is supported by the decrease in the alkalinity of the blood which has been observed in acute, as well as chronic, anæmia, by v. Jaksch,³³⁹ de Renzi,³⁴⁰ Peiper,³⁴¹ Kraus,³⁴² Rumpf,³⁴³ Drouin,³⁴⁴ Graeber.³⁴⁵ The decrease in the alkalinity of the blood is explained by Scherer³⁴⁶ from the appearance of lactic acid, acetic acid, and formic acid; by Mosler and Koerner³⁴⁷ from the formation of formic acid and lactic acid; by Bockendahl and Landwehr³⁴⁸ from lactic and succinic acid. Besides the organic acids mentioned v. Jaksch (*loc. cit.*) recognises in the appearance of uric acid

in the blood yet another reason for the diminution in the alkalinity of the blood.

Finally the increased toxicity of the urine of the anæmic is to be considered as a further symptom of the decrease of the intra-organic oxidation. Increase in the toxicity of the urine in anæmia has been demonstrated by Bouchard.³⁴⁹

Let us now find out theoretically to what extent the *Sperminum-Poehl* is capable of combating especially anæmia. The urinalyses made by Prof. Poehl furnish particulars.

As a ferment of the intra-organic oxidation *Sperminum-Poehl* produces in therapeutic employment an increase of Robin-Poehl's co-efficient of oxidation (*cf.* § 87). Beside, the use of Spermin is followed by a relative increase in the quantity of the chlorides, that is, in the proportion of the chloride of sodium to the amount of the urea increases (*cf.* § 88). The increase in the alkalinity of the blood which has been observed from the use of Spermin (*cf.* § 89) can easily be explained as owing to the oxidation of the organic acid which appears in the blood in anæmia, and which in the organism is burned up to carbonic acid (*cf.* § 80).

It is easily understandable that in anæmia (as well as in all other cases in which the action of Spermin has been studied) such oxidations distributed over the entire organism are not produced directly by the comparatively small quantity of *Sperminum-Poehl* introduced. The transient increase in the alkalinity of the blood, which appears with great regularity soon after the injection has taken place, suffices to procure favourable ground for the normal action of the physiological Spermin originating in the organism. By the combustion of the organic acids appearing in the blood of the anæmic it is not only the alkalinity of the blood that is brought nearer to the normal, but, owing to the increased processes of oxidation, the toxic intermediary products are also changed to indifferent compounds (*cf.* § 117). It has been demonstrated by Bouchard that the urine of the anæmic after inhalations of oxygen shows less toxicity than before. The significance of the intra-organic oxidation, that is its increase by therapeutic measures, has been fully appreciated by Lauder-Brunton³⁵⁰ and illustrated by a series of sympathetic experiments.

Of special interest are the observations of Dr. G. v. Hirsch already quoted (see p. 100), so far as concerns his having first

called attention to the appropriateness of the combination of iron with *Sperminum-Poehl*, with which he obtained very good results. These observations by Dr. Hirsch led to similar combinations (e.g., arsenic-preparations with *Sperminum-Poehl*) with which also favourable results have been obtained. A theoretical explanation of these therapeutic successes might be found in the fact that the leucocytosis which makes its appearance on the use of iron and arsenic is favourably influenced by *Spermin*.

When discussing the processes of oxidation in the organism of the anæmic we consider it necessary to point out that the condition of chronic anæmia and that consequent upon the loss of small quantities of blood in otherwise healthy individuals must be kept carefully apart. v. Noorden, however, in his "Lehrbuch der Pathologie des Stoffwechsels" (1893, p. 335) does not thus discriminate and therefore concludes, with but little justification, that the processes of oxidation are not decreased in chronic anæmia. For these conclusions he relies mainly on blood-letting experiments performed on animals. It is not surprising that even in these cases he found an increase in the intra-organic oxidation. Similar effects have also been often observed by Alb. Robin in human beings³⁵¹ after venesections, post menstrea, etc.; they can easily be shown to be attributable to the restitution-leucocytosis which appears after moderate loss of blood. Such a leucocytosis, however, has never been observed in chronic anæmia.

Nencki and Sieber³⁵² furnish us with direct proof that the intra-organic oxidation is decreased in one of the gravest forms of anæmia, viz., leuchæmia, by demonstrating that in leuchæmia much less of the unit of benzol given is oxidised to phenol than in healthy people. The action of the *Sperminum-Poehl* administered by means of injections and of the *Essentia Spermini-Poehl* on the metabolism and the blood in splenic leuchæmia has been observed by Prof. Senator and Dr Richter.³⁵³

(2) *Sperminum-Poehl* in Pulmonary Tuberculosis.

§ 121. Clinical
observations
on the
therapeutic
action of
Sperminum-

We will now proceed to consider the observations made on the therapeutic action of *Sperminum-Poehl* in pulmonary tuberculosis. The literature of the subject offers us so great a mass of material to work upon, that we cannot possibly analyse all

the cases presented to us ; we therefore confine ourselves to some of the most important of them.

Poehl in
pulmonary
tuberculosis

OBSERVATIONS OF DR. F. BUKOJEMSKI,³⁵¹ CHRONIC PULMONARY
TUBERCULOSIS.

CASE 1.—A., 32 years old, extremely emaciated. Skin and mucous membrane pale ; cough ; dyspnoea on insignificant movements ; appetite weak. In the right subclavicular region the sound was dull, the breathing had a bronchial character ; on the left side, too, some dulness with here and there slight rattling. In the apices the sound was dull and the bronchial respiration distinctly pronounced. On the right side of the back (downwards, from the lower border of the scapula) in places some rattling sounds which did not disappear during the coughing. Occasionally towards evening fever appeared, followed by night-sweats. The expectoration was muco-purulent ; tubercle bacilli were numerous. The patient had undergone medical treatment for four years. He used creosote, arsenic and iron. After sixteen injections of *Sperminum-Poehl* patient felt better ; appetite and digestion improved. Later the dyspnoea decreased, the rattling sounds in the lungs disappeared ; the patient commenced to inspire deeply without coughing. The treatment lasted forty-seven days and the patient, when he went home, had the appearance of a healthy man. The increase in weight amounted to eight pounds. Sleep was quiet, night-sweats were absent ; the temperature was normal. The expectoration was little and occurred only in the morning, it was mucous and showed no tubercle bacilli. The appetite was good, the stomach operated regularly. During the summer the patient took baths in the Dnieper. After six months the cough had ceased, weight increased, and the patient felt perfectly well. In this case the good results obtained with *Sperminum-Poehl* were very apparent.

CASE 2.—Chronic pneumonia. W., 40 years old, multipara, extremely emaciated, nearly complete disappearance of the panniculus adiposus ; skin and mucous membrane pale. Patient was extremely weak ; she could only walk short distances, when she suffered great anguish, pains in the chest, and dyspnoea. The expectoration was muco-purulent, very abundant, and contained many tubercle bacilli. All over both lungs, in front in the subclavicular region as well, as also along the axillary lines and along the back, rattling sounds could be heard which did not disappear during the cough. Only here and there there were places with rough breathing. The patient was free from fever ; sometimes, however, night-sweats appeared. Appetite very weak. Diarrhoea alternated with constipation.

Formerly the patient had been treated for three years by Dr. Bukojemski with creosote ; later, however, with injections of *Sperminum-Poehl*, only eight of which were administered in the course of a month. In this case also the specific tonic action of *Sperminum-Poehl* appeared after but four injections. One month after the injections the signs of improvement were as follow : Rattling sounds were yet perceptible in the subclavicular regions and in the right apex only, while in the left apex and in the other parts of the lungs the breathing was rough. Tubercle bacilli were found in very small numbers. The strength of the inspiration and expiration was considerably increased. The patient was much stronger ; she no longer became tired when walking. Her appetite was good and the bowels operated daily and normally. In the course of the year the patient drank much milk and took no medicine what-

ever. In the summer there were still some rattling sounds in the apices (in the left hardly audible) and in the subclavicular regions. Patient coughed little; the expectoration in the morning was only more plentiful, with little admixture of pus. Very few bacilli were present. No full cure was possible; still, the patient had a good appetite; the bowels worked regularly so that aperients were not needed more than once a week. Patient had gained three pounds in weight and felt generally so very well that she wanted no further treatment and commenced to busy herself with light domestic work.

OBSERVATIONS OF DR. J. OSTROUMOFF,³⁵⁵ CHRONIC PNEUMONIA,
HEMIPLEGIA AND CATARRHAS PULMONUM CHRONICUS.

The patient, G. B., 56 years old, was fairly strongly built and of average appearance. Four years ago he suffered with croupous pneumonia and a year and a half later had a stroke of apoplexy with temporary loss of speech (the mouth was drawn to the left and the point of the tongue to the right), with paresis of the left upper and paralysis of the left lower extremity. In September of the same year, before the patient had recovered from the first stroke a second followed, which nearly caused death. Patient remained for nearly a year in bed, with fully paralysed lower and paresis of the upper extremities, accompanied by a disturbance of speech which made his words indistinct and difficult to understand. Later he regained the use of his hands. Even with the assistance of his nurses, by supporting him under the arms, he could scarcely move his feet. After the second stroke, at intervals a pronounced constipation set in. Further, in September 1893, a catarrhal condition of the apices of the lungs appeared, with vehement cough and purulent expectoration. Towards evening the temperature rose to 39°, accompanied later by slight night-sweats. In the right subclavicular region the sound was dull, the respiration having a bronchial character—in the left there were numerous rattling sounds. During the following October the strength of the patient became considerably less. He had to stay for hours in bed and his condition was sometimes so low, that his friends feared for his life. He became apathetic and forgetful, and had the appearance of an atrophic and exhausted old man.

Under these circumstances in November of the same year, on account of the inefficacy of the means previously employed, treatment with *Sperminum-Poehl* was commenced and proved very successful. Within a short time the general condition of the patient was much improved. The pulmonary catarrh diminished; the feet became more steady. The patient could stand and walk with but little support from others. Instead of his former apathy he now became fresh and lively.

OBSERVATIONS OF DR. A. PODKOPAJEFF,³⁵⁶ PULMONARY
TUBERCULOSIS.

CASE I.—The patient, N., female, 26 years old, suffered with tuberculosis of the lungs. Pronounced dullness and pains in the apices of the lungs, especially in front and behind; many rattling sounds; the sputum was dirty with typical pus-balls, and on examination showed tubercle bacilli. The temperature was rising. Extreme weakness, anorexia, and profuse night-sweats were present with great emaciation.

On the day of the first injection of *Sperminum-Poehl* February 26, 1892, the pulse was 102, and the patient very weak with profuse night-sweats. After but ten injections the temperature approached the normal. The patient gained in strength; the cough troubled her but little; the rattling sounds had almost disappeared. Slight transpiration. The pulse was full, up to 80 beats

per minute. Patient ate with enjoyment and asked for different kinds of food. On further treatment the night-sweats stopped almost entirely.

CASE 2.—Pulmonary tuberculosis. Pat. T., 27 years old, more than average size; with a flattened, poorly developed chest. The right lung was chiefly affected. Supraclavicular region sharply sinking in. Respiration with bronchial sound. The examination of the sputum showed the presence of tubercle bacilli. At the end of October 1893, the patient contracted a severe cold. There was much rattling sound in the left lung. The temperature was feverish with slight remissions in the morning. At noon and in the evening it rose to 37° and 40°. In the night profuse sweating was present, with failing in strength; pulse 120 a minute. Appetite almost entirely gone. As the customary treatment—inhalations of creosote-vapours with balsamic means; and creosote internally, guaiacol with fever-remedies of antipyrin and salicylate of quinine, as well as inunctions with turpentine, creosote and lanoline—gave no favourable results, injections of *Sperminum-Poehl* were prescribed. Twelve injections were made. After but four injections the patient felt hungry, and the transpiration decreased considerably. The pulmonary symptoms improved visibly; the rattling sounds became less numerous; the expectoration was purer and more liquid. The pulse became fuller and slower: 80–82 beats. The temperature sank towards morning to the normal and rose between 2 and 3 o'clock P.M., and towards 11 P.M., to 38° or 38° and a few tenths. Further injections again increased this improvement and finally the sweating ceased entirely. The general condition was much better; the sleep good; the cough was far less troublesome; while the expectoration was much diminished. Walking in the open air was permitted to the patient. In the face of this improvement the injections were stopped, being repeated after a short respite. During the injections guaiacol was given and the inunctions were continued. Milk and cognac were plentifully given.

From the end of January 1894, to March 16, 1895, Dr. Podkopajeff gave the patient twelve injections of *Sperminum-Poehl*. Patient felt very well, became lively, and was daily in the open air; the temperature became normal, the dyspnoea very trifling. Rattling sounds were absent, the sputum on awaking in the morning was quantitatively insignificant; appetite and sleep were both good. The nutrition was considerably improved, and at the same time there was an increase in his weight. Patient could resume his daily occupation (at the time he was a restaurant-keeper). He stood the injections all the time very well, without pain, without local symptoms of irritation or inflammatory changes of the skin.

CASE 3.—Pulmonary tuberculosis. The patient, a lady, 32 years old, was of medium size, of weakly constitution, with a hollow, narrow chest. The fat-tissue was extremely atrophic. The right apex of the lungs and the right middle lobe were the parts most affected. Pains, a distressing cough, much secretion of a purulent, ill-formed sputum were present. At the examinations made at the end of 1892 and 1893 tubercle bacilli were found. The sleep was poor on account of the cough. Pulse, 102; but little night-sweat. The results of twelve injections were: increase of the subjective feeling, well and better appetite; improvement of the pulmonary symptoms. Change, improvement and diminution of the sputum. The pulse became quite full and normal. Rattling sounds and dyspnoea almost disappeared. The temperature became normal.

After a cold the symptoms of the chest affection became worse. Inflammatory symptoms of the throat and larynx were added; the temperature rose; the patient had for a few days to stay in bed. Night-sweats did not

appear on this occasion; the other symptoms, however, were the same as at the beginning of the injections. After four injections of Spermin a considerable improvement was observable; the expectoration became thinner; it was brought up more readily; the general condition improved; the patient was more lively as well as stronger. Appetite and sleep improved; the rattling sounds disappeared. The respiratory movements became deep. The strength increased considerably. After a fortnight the patient was lively and quite strong. The sputum was watery and small in quantity. During the injections Dr. Podkopajeff prescribed for the patient an ointment of turpentine and creosote with cod-liver-oil and guaiacol and terebene in pills alternatively. As a narcotic he gave codeine gr. $\frac{1}{4}$ occasionally. Good food and a mixture of barley and milk were taken. Towards the end of the treatment only a slight increase in the weight was found.

CASE 4.—Pulmonary tuberculosis. Patient, F., 19 years old, was of medium size, poorly nourished; the skin and the mucous membrane were pale; the appearance cachectic; the chest hollow and narrow. The cough was strong with secretion of a yellowish, sometimes thick and dirty, sputum in which elastic fibres and tubercle bacilli were found in large numbers. The left side was especially affected. There was considerable catarrh of the throat and the posterior wall of the pharynx, which also extended to the larynx. The voice was hoarse. The urine, 500 ccm., was cloudy; it reacted acid; specific gravity, 1.008. The sediment consisted of mucus with pavement epithelia. The proportion of the quantity of the uric acid to that of the phosphoric acid in the form of di-sodium phosphate was $0.24 : 0.56 = 0.43$, which, according to Zerner indicates an excretion of uric acid exceeding the normal. Albumen was not found; of pepton, however, there were slight traces. The proportion of the total of N in the urine to the N of the urea was $5.57 : 5.04 = 100 : 90.48$, from which it follows that the intensity of the oxidation of the nitrogenous substances remained below the normal.

After ten injections the appearance was fresh and lively; strength and appetite very good. In the left apex insignificant rattling sounds, but otherwise pure vesicular breathing. The sputum was but small in quantity, watery, and quite pure; the cough did not disturb the patient. The urine was secreted very easily; it was pure and reacted a little acid. For a fairly lengthy period the patient felt very well. His appearance was fresh and strong. Appetite and sleep were both good. In the affected place of the left lung Dr. Podkopajeff found vesicular breathing, but weaker and rougher than on the right side, while cough was not present. To increase the oxidation in the organism, the patient was given twice a day twenty drops of *Essentia Spermini-Poehl* in Borshom water (Katharina Spring). Under the influence of the Spermin treatment the intraorganic oxidation and the textural respiration showed a striking tendency towards improvement. This was especially indicated by the proportions of the urea to the chloride of sodium, which was determined in the following four analyses: (1) $10.8 : 3.38$, or $100 : 31.8$; (2) $13.00 : 5.74$, or $100 : 44.2$; (3) $6.35 : 2.87$, or $100 : 45.4$; and (4) $11.81 : 14.04$ or $100 : 114.1$.

From what we have here said, it will be seen that the improvement in the general condition of the patient was in perfect agreement with the objective data of the urinalyses.

CASE 5.—Tuberculosis of the lungs and the larynx. Patient, P., 32 years old, an official, suffered with chronic tuberculosis and hemoptœa. His appearance was extremely emaciated and cachectic. Exacerbating fever, serious night-sweats, typical symptoms of the pulmonary tuberculosis were

present; to which was added a tuberculous inflammation of the larynx. As the usual method of treatment was altogether unsuccessful, after ten days the patient was given *Essentia Spermini-Poehl*, beginning with twenty drops once a day, later twice in Borshom water. Some time after the use of Spermin everything went much more favourably. The appetite improved, as well as the general condition, and the strength increased. The temperature subsided almost to the normal; the night-sweats first decreased and then disappeared almost entirely. Cough and expectoration were much diminished; while the sputum was more watery and much cleaner.

OBSERVATION OF DR. W. KLIMONTOWITSCH,³⁵⁷ CHRONIC PNEUMONIA.

Patient, 43 years old, extremely exhausted (chronic tuberculosis), with immense enlargement of the cervical and axillary glands. Much purulent sputum, heavy night-sweats, frequent diarrhoea, itching of the whole surface of the body were present. After four injections of Spermin (day after day) the fever decreased, the cough almost entirely disappeared, and the expectoration decreased in quantity (muco-purulent). The night-sweats ceased, appetite and digestion improved, and the patient felt stronger. The itching of the skin during the night subsided, the glandular enlargement decreased fully one half; while the rattling sounds and dyspnoea became less.

OBSERVATION OF DR. E. MORITZ,³⁵⁸ PULMONARY TUBERCULOSIS.

Patient was 54 years old. Emphysema with phthisis tuberculosa pulmonum. The changes were very extensive. The expectoration was plentiful, muco-purulent; the weakness produced perfect anorexia. Forty-five injections of *Sperminum-Poehl* had some effect, though not of a lasting character. At first the patient was refreshed and felt an increase of strength. Because, however, of the advanced stage to which the tuberculosis had attained, the disease did not yield to the treatment.

OBSERVATION OF DR. E. V. ROSSI,³⁵⁹ ST. PETERSBURG, IN THE INFIRMARY OF THE REGIMENT OF GUARDS OF FINLAND.—PLEURITIS EXUDATIVA SINISTRA.

Patient was 22 years old. After thirteen injections of *Spermin* the re-absorption of the pleuritic exudation commenced and the fever ceased. The quantity of the leucomaines went back from 3.75 per mille to 0.15 per mille. The proportion of the total nitrogen to that of the urea before the injections was 100.83, and increased after them to 100.86.

OBSERVATION OF PROFESSOR W. STANGE,³⁶⁰ PULMONARY TUBERCULOSIS.

Patient P. after twenty-two years had for the first time hemoptoea which, when he handled chlorine, repeatedly occurred. In January 1896, hemoptoea again appeared, the first time after a lecture lasting three hours. From March 18-20 it appeared again (in Mentona). After his return to St. Petersburg in April, the patient received daily an injection of *Sperminum-Poehl*. In June and July he took the waters at Ems. During this time he tried to discontinue the injections of Spermin. Within three days, however, night-sweats appeared, which ceased as soon as he recommenced the injections. From February to December 1897 he took guaiacol in doses of 0.3 to 0.5 two, three, or four times a day. In June 1896, hyaline cylinders appeared intermittently in the urine, being present, however in increased quantities during disturbances of the function of the bowels. From the urinalysis it became

clear that the appearance of the hyaline, occasionally finely granulated, cylinders coincided with the presence of an increased amount of indican and ether-sulphuric acid. As it was supposed that the guaiacol in this case produced irritation of the kidneys, it was replaced by Peru balsam (0.2 to 0.3). In June to September–October 1897, hemoptœa appeared several times; four or five injections of Spermin a day were given. General condition good; perfect ability to work. Bacilli usually present—twice only in the winter of 1898 were no bacilli found. Sputum was once tainted with blood—April 1898. During the whole time treatment with Spermin was continued, that is, there was either an injection of *Sperminum-Poehl* made every day or twenty to thirty drops of *Essentia Spermini-Poehl* were given two or three times a day. In 1899 the examination of the sputum for tubercle bacilli often gave negative results. In the following year the tubercle bacilli disappeared entirely. The use of Peru balsam was discontinued while the treatment with Spermin was kept up. During the following years hemoptœa did not appear, nor were tubercle bacilli found in the sputum.

§ 122. Explanation of the therapeutic action of spermin in pulmonary tuberculosis

From these facts but one conclusion can be drawn, viz., that all the authors referred to can establish the favourable influence of *Sperminum-Poehl* on the course of tuberculosis. *Sperminum-Poehl*, of course, does not cure such patients, but it produces considerable improvement of the general condition. Besides, *Sperminum-Poehl* also causes the removal of several troublesome symptoms of tuberculosis.

(1) It is established that *Sperminum-Poehl* not only diminishes night-sweats, but in some cases stops them altogether.

(2) Variations in the temperature disappear, and the temperature approaches the normal.

(3) The severe cough diminishes.

(4) The discharge of sputum is relieved and quantitatively diminished.

(5) The appetite returns.

(6) Weight and strength increase.

To judge, therefore, from all that has been said, such a remedy as *Spermin* should not be overlooked. It gives great relief to unfortunate sufferers from various serious diseases; a relief that can only be given by a physiological tonic like *Spermin*. True, that with *Sperminum-Poehl* some of the patients received creosote and guaiacol, in addition to nutritive food. Yet we have every reason to believe that the results obtained are to a very large extent principally attributable to *Sperminum-Poehl*, because all the remedies used previously to its employment, although not entirely useless, proved to be of little effect.

Although pulmonary tuberculosis has its place among the

infectious diseases, the observations on consumptives have been taken in the group of inanition-diseases, because the action of Spermin, though not noticeably in most cases influencing the amount of the bacilli as well as the local symptoms, in the pulmonary tissue has a decidedly favourable influence on the metabolism in the matter of nutrition. In this way the action of Spermin gives similar results to those observed in anæmia, and hence the same signs are present for the use of this means.

The method of treating tuberculosis with raw meat, which was advised by Ch. Richet and Chantemesse, doubtless in some cases gives very good results. Whether here, as Bouchard claims, we have to deal with an over-feeding cure or not (the latter view being held by Furster), we do not decide. At any rate, in the use of raw meat we have the introduction of fairly large quantities of animal textural juices with active hæmoglobin, or, in other words, simultaneously with good nutrition oxydases are brought into the body. Therefore this method of treatment, which, by the way, can only be employed where the meat is subject to a thorough inspection, is almost identical with the Spermin Therapy.

The influence of the injections of Spermin on the night-sweats of the consumptive is altogether characteristic. According to the unanimous statements of Prof. Stange, Drs. Pantshenko, Bartoschervitsch, Podpokajeff, Cohn, Maximowitsch, Bukojemski, and others, the use of *Spermin* causes a noticeable diminution in the frequency and intensity of night-sweats (*cf.* § 113).

Prof. Pochl has, by urinalysis, very thoroughly investigated the influence of *Sperminum-Pochl* on the metabolism of the consumptive. The numerous urinalyses executed by him during many years demonstrate that the intermediary products of the metabolism appear in the urine of the consumptive in comparatively greater quantities. This statement is also confirmed by v. Noorden,³⁶¹ and Gerdes. The increased amount of leucomaines accounts for the constantly observed, though not always considerable, decrease of the co-efficient of oxidation of Robin-Poehl. According to Poehl the proportion of the urea to the chloride of sodium, however, is comparatively little, if at all, changed. V. Noorden also finds that the chloride of sodium balance in phthisis is normal. The

alkalinity of the blood, according to Rumpf³⁶² and Drobny,³⁶³ is decreased in pulmonary tuberculosis.

We must not refrain from mentioning the recent article of Prof. Duerck,³⁶⁴ who has demonstrated that the normal lung of man is by no means an organ free from germs, but, like the alimentary canal, it contains on its surface different germs which, by themselves, are quite harmless parasites, and whose presence is by no means sufficient of itself to produce pathological changes of the organism. When, however, the organism is by over-fatigue, inanition—that is, by acidulation of the textural juices, or by cold—disturbed in its metabolism, the parasites in the lungs are provided with an opportunity to attack the tissues with a simultaneous display of qualities producing inflammation. The experiments cited in chap. v. demonstrate that *Sperminum-Poehl* removes the noxious forces in over-fatigue and inanition, and decreases the virulence of some micro-organisms. These physiological chemical facts demonstrate that the therapeutic employment of *Sperminum-Poehl* in consumptives has not only a practical, but a physiological-chemical foundation.

(3) *Sperminum-Poehl* in Typhoid Fever.

§ 123. Clinical observations on the therapeutic effects of *Sperminum-Poehl* in abdominal typhoid fever.

The favourable therapeutic action of *Sperminum-Poehl* in typhoid fever has been observed by many authors; as, Roschtschinin, Klimontowitsch, Podkopajeff, Pantschenko, Hildebrandt, Epifanoff, in the clinics of Prof. L. W. v. Popoff, and others.

We will first study carefully a case of Dr. Hildebrandt's from the St. Petersburg Naval Hospital, because it presents all the features of a severe auto-intoxication.

OBSERVATION OF DR. HILTEBRANDT.³⁶⁵ TYPHOID FEVER. (RECONVALESCENCE.)

Patient had gone through a severe case of typhoid fever followed by feverish delirium and coma lasting several days. The action of the heart was weak, and required stimulants from the beginning. Towards the end of the fifth week the case was complicated by the addition of double-sided otitis media. The failing in strength increased progressively, and was aggravated by the patient's vomiting as many as five times a day for ten days, without any symptoms from the peritoneum. Occasional chills, sometimes followed by sweat, led to a suspicion that it was a case of malaria, and arsenic was prescribed internally, as well as in the form of hypodermic injections. Occasional spells of bronchitis suggested that tuberculosis might be present, and, in spite of the negative results of the examination of the sputum for tubercle bacilli, creosote, carbonate of guaiacol, and kreosotal were given alternately. In the sixth month after

his entrance into the hospital the patient was merely a skeleton covered with skin. He could not sit up in bed save with assistance, and then for a few moments only, as severe dizziness, nausea and a condition approaching fainting appeared. Food was taken only in a recumbent position, while the patient remained otherwise perfectly apathetic. Notwithstanding the very varying methods of treatment, the condition of the patient continued to be of an exceedingly desperate nature. Some two months later the feverish condition was aggravated by the otitis and the appearance of some very painful furuncles in the auditory canal of both ears.

The theory that a ferment of intraorganic oxidation existed, together with the claims made by Prof. Pöchl concerning the great value of *Spermin*, and finally the daily increasing accumulation in observations which seemed to confirm the favourable results to be obtained by the use of *Sperminum-Pöchl*, all suggested to Dr. Hildebrandt the idea that this patient would be a very proper subject upon whom to try the efficacy of *Sperminum-Pöchl*.

In the course of three weeks twenty-five injections were made; all other remedies being discontinued. After the tenth injection the patient himself declared that "his head felt much clearer." He now took his meals resting on his elbow, not recumbently as previously, and his appearance gave signs of considerable improvement. While he took the first injections quite apathetically, as though he had lost all sensibility, from now onwards he felt but little pain. After twenty-seven injections he stood up, regardless of the prohibition of his physician. Assisted by his people on the following day, he began to walk. The injections were then discontinued. The good condition of the patient nevertheless continued. The weight of the body, as could be plainly seen, increased uninterruptedly, so that from a mere skeleton he became a rejuvenated being, with a marked increase of adipose tissue. A week later, regardless of the strictest injunction, he stood up alone in the night and walked some fifteen steps without assistance. Contemporaneously with the improvement of the general condition, the excretion of the urine had also quantitatively improved. Before the injections the quantity of the urine rarely reached 1000 ccm.; after the injections of *Sperminum-Pöchl* it ranged about 1500 ccm. The little clouds of mucus which had previously been present now disappeared and the reaction, which was sometimes alkaline, occasionally neutral, or only very weakly acid, became permanently acid. The urine preserved itself noticeably longer, while previously alkaline fermentation quickly appeared. The coefficient of the energy of oxidation rose from 68.2 to 87.17.

During the two following months there was again a tendency in the weight of the body to decrease noticeably, accompanied by a more feeble appearance of the patient. As no objective changes could be established, Dr. Hildebrandt recommenced with the injections of *Spermin*, of which altogether he made twenty. The patient was once more strengthened, so much so indeed that he was able to be sent home.

OBSERVATION OF DR. ROSCHTSCHININ.³⁶⁶ TYPHOID FEVER. CROUPOUS PNEUMONIA AND WEAKNESS OF THE HEART.

Patient had gone through an attack of typhoid fever, complicated with croupous pneumonia. Small, frequent pulse, much failing in strength, together with great emaciation of the body, left but little hope of a favourable course of the disease. Heart-failure was to be expected. After treatment with injections of *Sperminum-Pöchl* the pulse became fuller and an improve-

ment took place in the general condition. The further course of the disease was not marked by any special event, although the croupous pneumonia did not entirely disappear. The fever continued. It had, however, assumed a different character. Several months later the pathological process had not yet disappeared. The percussion showed dulness on the right shoulder-blade, the auscultation a subcrepitant sound. On account of the weakness of the patient, it was decided to renew the injections of *Sperminum-Poehl* as the patient had "suffered from sleeplessness since the injections had been discontinued."

OBSERVATION OF DR. KLIMONTOWITSCH.³⁶⁷ CONDITION OF INANITION
AFTER TYPHOID FEVER.

Patient was 19 years old. Condition of inanition lasting three weeks after a severe case of typhoid fever. Temperature 36 to 36.5°; pulse 56 to 54—filiform. Aphasia; paresis of the extremities; tremor of the head *Incontinentia urinæ et alvi*. Immediately after the first injection of *Sperminum-Poehl* pulse was 66 to 68 (fuller); temperature 37.5. After the others there was a general disappearance of all the symptoms of inanition.

The beneficent action of *Sperminum-Poehl* appeared in the cases here mentioned in so characteristic a manner that further discussion seems altogether superfluous. The facts in the cases cited speak for themselves eloquently enough to make any further explanation unnecessary.

And here it should be remarked that in Dr. Hiltebrandt's case, which resulted in the quick and lasting return of the strength of a patient whose comatose condition had lasted more than six months, the idea of suggestion is altogether excluded. The appearance of the same results after repeated treatment is a fact which, together with the other observations as to the effects of *Sperminum-Poehl* in typhoid fever, should be sufficient to convince the greatest sceptic.

In connection with these interesting observations we would like to point out that according to Poehl's experience in typhoid fever the relative quantity of the nitrogenous intermediary products of metabolism is always increased. These experiences are in full agreement with the observations made in typhoid fever by Gumlich³⁶⁸ and Kobin.³⁶⁹ Consequently the use of *Sperminum-Poehl* is indicated in typhoid fever also on urosemiotic grounds.

(4) *Sperminum-Poehl* in *Marasmus senilis*.

The action of *Sperminum-Poehl* in *marasmus senilis* has been observed by the following authors: Dr. Shichareff, Dr. Bukojemski, Dr. J. Maximowitsch, Dr. G. v. Hirsch, Dr. F. Krieger, Dr. J. Postojeff, Dr. Tjasheloff, Dr. Mrotsch-

kowsky, Dr. Viktoroff, Dr. Moritz, Dr. Frétin, as well as many others.

Sperminum-Poehl in
marasmus
senilis

OBSERVATION OF DR. S. SHICHAREFF.³⁷⁰ MARASMUS SENILIS.

Extremely emaciated and weak man of 63 years; apathetic to all his surroundings; not capable of following conversation or reading even for a short time. Movable psuedarthrosis in the upper third of the right tibia and intense atrophy of the muscles of the same extremity, as a result of which only slow walking was possible, and that only with great difficulty and the assistance of two sticks. After eight injections of *Sperminum-Poehl* in the course of a month the patient was so much strengthened that he could walk fairly well supported by a stick, while for short distances he could manage even without a stick. Under the influence of *Sperminum-Poehl* he acquired an interest in his surroundings and began, without getting tired, to read and take part in conversation for several hours. Further, after the injections, erections occurred several times in the morning—an event that the patient had not observed for two or three years previously. The tonic action of the *Sperminum-Poehl* lasted, as in one of the cases previously reported, more than two months and when it became weaker at the end of the third month two further injections restored the strength.

OBSERVATION OF DR. BUKOJEMSKI.³⁷¹ MARASMUS SENILIS.

Miss M. K., 95 years old, virgo intacta; arteriosclerosis well pronounced; appetite and digestion weak; constipation. Patient was deaf without any visible changes in the ears. For many years patient had pains in the back, especially when walking, which always made her tired and weak. For the last four years she had suffered each spring with intermittens quotidianae. The disease lasted each year about a month and a half, and terminated with the appearance of warm weather. After eight injections of *Sperminum-Poehl* the hearing was much improved. The pains in the back which had been in existence for about fifteen years, and had defied all the remedies employed, disappeared entirely, so that they were not even noticeable during walking. Her general condition improved considerably, the appetite became better and the old woman became again able to move about. In the beginning of spring the customary yearly fever did not appear. As the hearing, however, became a little poorer and at times some pains reappeared, four more injections of *Sperminum-Poehl* were administered. The general condition, appetite, and hearing again improved considerably, the pains disappeared, and the improved condition lasted till the fall. Six months later eight more injections were made after which no fever appeared, the old woman heard well, had only insignificant pains in the back, and even those only after longer spells of walking. The appetite became good; the patient felt generally better and suffered no more from the former weakness.

OBSERVATIONS OF DR. J. MAXIMOWITSCH.³⁷² MARASMUS SENILIS.

The most clearly evident effect was obtained by Dr. J. Maximowitsch with *Sperminum-Poehl* in a sixty-two-year-old individual in the stage of convalescence from croupous pneumonia. The failing in strength had gone so far that the patient could hardly go from her bed to an armchair. Injections of Spermin were made once a day for eight days, later on every second or third day, and altogether twenty-four injections of *Sperminum-Poehl* were administered. Patient improved during two months quite extraordinarily;

he gained in weight nearly twenty pounds, and declared that for fifteen years he had never felt so well as recently.

In three similar cases Dr. J. Maximowitsch used *Sperminum-Poehl* in old people on their urgent demand for the purpose of raising their strength and appetite, as well as relieving dyspnœa, a consequence of emphysema of the lungs and arteriosclerosis. In all these cases he observed an improvement which lasted for from one to four months after the injection.

OBSERVATION OF DR. A. BOGUSCHEWSKY.³⁷³ MARASMUS SENILIS.

In General B., 70 years old, the first symptoms of marasmus appeared. The gait was slow. Any physical exertion caused the patient to tire rapidly, and in the daytime he always left sleepy. The hearing on both sides was weakened, the sight was also poor. Sleep and appetite were affected. The bowels were atonic and only operated with the assistance of physic. The patient complained of agonising pains—which appeared spontaneously—in the right eyeball, the orbita, and its neighbourhood. The eyeball was rather enlarged, very hard, and protruded slightly from the orbita. Dr. Tichomiroff and later Professor Dohnberg, who were called into consultation, demonstrated the existence of a glaucomatous process which led to the suggestion to use cocain and pilocarpine. As, however, the process did not recede, Professor Dohnberg proposed, as a radical measure, enucleation of the right eye. The age of the patient, his unsatisfactory general condition, and the necessity of performing the operation under chloroform-narcosis, induced Dr. A. Boguscheski to prepare the patient for the operation by hypodermic injections of *Sperminum-Poehl*. Twelve injections were made and the patient withstood the operation splendidly. The operation was a striking success, thanks to the great ability of Professor Dohnberg. The period after the operation passed favourably, while the healing of the wound and the recovery of patient occupied but little time. Patient gladly and repeatedly said that he now hardly recognised himself. He had become strong; his appetite and sleep had considerably improved; his general condition and frame of mind were excellent. Since the injections the patient undertook very extended promenades in the city, while before then even short distances had made him tired.

OBSERVATION OF DR. G. v. HIRSCH.³⁷⁴ MARASMUS SENILIS.

Dr. G. v. Hirsch noted the favourable influence of *Sperminum-Poehl* in a case of marasmus and arhythmia of the heart in a seventy-year-old diplomat who felt perfectly well after the use of *Essentia Spermini-Poehl*.

Other cases of marasmus senilis observed by other authors and described in a similar manner, all demonstrate the favourable stimulating effects of *Sperminum-Poehl* (in the form of injections as well as drops) on the enfeebled human organism.

As in the organism the natural producers of Spermin, *i.e.*, the glands (testicles and ovaries in the first place), discontinue their activity in senility, the spermin therapy is, according to Professor Hansemann, indicated by this alone in the sense of Substitution Therapy.

Professor N. Fenomenoff first observed in an artificial climax (after ovariectomy) the favourable action of *Sperminum-Poehl*. Professor Landau accounted for the effects of Ovariin tablets after such operations to the contents of Spermin in the ovaries, which is in full agreement with the foregoing statements.

§ 125. Explanation of the therapeutic effects of *Sperminum-Poehl* in marasmus senilis

The urinalyses clearly demonstrate in marasmus senilis a decrease of the intraorganic oxidation which is to be explained by the obliteration of the physiological sources of Spermin. Finally the more or less pronounced arteriosclerosis, which so often accompanies the marasmic conditions, are to be looked upon as one of the forces which have to be considered in therapeutics.

(5) *Sperminum-Poehl* in infants, especially the prematurely born.

OBSERVATIONS OF DR. N. KOROLEFF.³⁷⁵

Dr. N. Koroleff has used *Sperminum-Poehl* internally in a few cases in infants. It proved less effective than did *Sperminum-Poehl* in other cases in the form of hypodermic injections. Used internally, he obtained in two cases a temporary improvement from *Sperminum-Poehl*; in two others, however, failure resulted. It should be stated that only the gravest forms of disease in which the customary means had failed to operate were selected for the observations with *Sperminum-Poehl*. In many only one or two injections could be made. Among the infants treated with *Sperminum-Poehl* there were many prematurely born of whom some had no special disease, and they strikingly recovered. In cases of acute enteritis and even in some of cholera morbus striking improvements and quick recoveries were obtained. In prematurely born infants good results can occasionally be obtained. Still, one should not delay until the failure of all other means, but should at once treat the little ones with *Sperminum-Poehl*.

§ 126. Clinical observations on the therapeutic action of *Sperminum-Poehl* in prematurely born infants

(6) *Sperminum-Poehl* in Rickets.

OBSERVATIONS OF DR. MALINOWSKI.³⁷⁶

Here we have to note the observations of Dr. Malinowski which testify to the favorable effects of *Sperminum-Poehl* in rickets. Of the cases observed by him the author reports but one in which after the employment of *Essentia Spermini-Poehl* an apparent improvement was established when the generally adopted methods of treating rickets (unfortunately, he does not state how long they had been employed) had given but very insignificant results.

(7) *Sperminum-Poehl* in skin-diseases.

OBSERVATION OF DR. OSTROUMOFF.³⁷⁷ ULCUS CRURIS ET PEDIS.

Patient suffered for many years with chronic articular rheumatism the indelible results of which were plainly evident in the form of thickening of the ends of the bones. An ulceration, which as a result of this had developed on the outside of the left leg, did not show the least improvement in spite of the most varied and careful treatment. Later, after the employment of antiseptic means, an improvement in the condition of the ulceration was noticeable :

§ 127. Clinical observations on the therapeutic action of *Sperminum-Poehl* in skin diseases

it became cleaner; the discharge of pus lessened; the circumference of the ulceration, however, as well as the sensitiveness, remained unchanged. In face of these facts, especially for the purpose of influencing the nervous system of the patient, during the following month three injections of *Sperminum-Poehl* were given. The local treatment remained unchanged. The result was: disappearance of the painfulness of the ulceration and diminution of its circumference by one-third. At the same time the general condition also of the patient improved: appetite and sleep became good, and the irritability disappeared. Thus three injections of Spermin, made in the course of four or five weeks, effected the healing of a large ulceration which had lasted three years.

OBSERVATIONS OF DRs. PROCHOROFF, SHICHOWEFF, HUEBBENET, DE BUCK, AND DE MOOR.

Dr. Prochoroff,³⁷⁸—Atonic ulcerations in an old man. Unsuccessful treatment during a period of two months and a half. After two injections of *Sperminum-Poehl* healing of the ulcerations took place in three weeks by means of local treatment.

Following the use of *Sperminum-Poehl* in four cases of psoriasis vulgaris and two of pityriasis, Drs. Shichareff and Huebbenet³⁷⁹ observed in addition to a diminution of the local pains, a strengthening influence on the organism which showed itself in a considerable increase of the muscular strength of the upper extremities (dynamometrically), as well as in other ways.

Drs. de Buck and de Moore³⁸⁰ by the use of *Spermin* in psoriasis guttata obtained a cure within a fortnight, after all the customary means had been employed without success.

OBSERVATION OF DR. SYMONS-ECCLES. PSORIASIS.

Dr. Symons-Eccles³⁸¹ reports a case of inveterate psoriasis in which after the hypodermic injection of *Sperminum-Poehl* a "striking" diminution of the symptoms present with arrest of the process was observed.

OBSERVATION OF DR. BOSSE.³⁸² PRURITUS SENILIS.

Dr. Bosse obtained some splendid results with *Sperminum-Poehl* in two cases of pruritis senilis which had lasted for years. One of his patients was freed from his suffering even with the first injection. In another the itching first increased, but disappeared entirely after four injections.

§ 128. Explanation of the therapeutic action of *Sperminum-Poehl* in skin diseases

We have included the skin diseases in the group of the conditions of inanition, because in all these cases, besides the unequal etiological factors (disturbances of the circulation, nervous irritation, infections, different auto-intoxications, etc.), there are always some disturbances of the nutrition present which, as in the other representatives of this group, are characterised by a decrease of the intraorganic oxidation and the alkalinity of the blood.

The urinalyses in chronic skin affections, as, for instance, psoriasis, chronic eczema, herpes zoster, pemphigus, indicate

a decrease of Robin-Poehl's coefficient of oxidation. As to the alkalinity of the blood in skin diseases, the investigations made by Dr. Tschlenow³⁸³ in the clinic of Professor Pospisilow on thirty patients gave the following results :

(1) The alkalinity of the blood is normal in some superficial or merely local skin diseases (herpes tonsurans, scabies, alopecia areata, lupus vulgaris, lupus erythematosus, tuberculosis and atrophy of the skin).

(2) In some deeper-seated dermatoses, in which the presence of disturbances of the general condition might be supposed (dermatitis herpetiformis, purpura hæmorrhagica, subacute and chronic eczema, erythrodermia, pemphigus, lichen ruber acuminatus, elephantiasis, and psoriasis), however the alkalinity of the blood is decreased.

Professor Polotebnoff was the first to oppose the view that psoriasis and other dermatoses should be considered as merely local diseases of the skin. That we have rather to deal with an auto-intoxication, is demonstrated by the observations of Professor Polotebnoff who connects the appearance of the psoriasis with that of the "rheumatic diathesis." Therefore Le Roy Satterbec considers defective oxidation and accumulation of uric acid in the organism as causal factors and treats the patients accordingly. This opinion is also endorsed by Eger.³⁸⁴ From this point of view the results so far obtained with the Spermin Therapy in skin diseases are easy of explanation.

II. Anomalies of the Metabolism.

(1) Sperminum-Poehl in Uric Acid Diathesis.

ARTHRITIS DEFORMANS, RHEUMATISM, ENDARTERITIS DEFORMANS.

The uric acid diathesis with all its different forms is characterised above all by a typical auto-intoxication. Therefore by the employment of the *Sperminum-Poehl* in the form of hypodermic injections, as well as internally, favourable results are obtained. In the literature on the subject we find a large number of observations made by different authors—e.g., Frétin, Pantschenko, Goldberg, Prof. Affanasjeff, Prof. Schapiro, Dr. Prochoroff, Dr. G. v. Hirsch, as well as many others.

§ 129. Clinical observations on the therapeutic action of Sperminum-Poehl in uric acid diathesis

OBSERVATION OF DR. FRÉGIN (PARIS). CHRONIC ARTICULAR RHEUMATISM.

Patient, a 63-year-old woman, suffered with chronic rheumatic contraction and malformation of all the joints, together with extreme general emaciation and disuse of all the functions of the body: she was a specimen of those helpless old women who in great numbers people the asylums. The appetite was almost entirely wanting; mobility was to such an extent weakened that the patient could hardly go across the street. She complained of pains in all her joints and suffered with sleeplessness. At the dynamometer, before the injections of Spermin she with difficulty reached 14°. Four injections of *Sperminum-Poehl* were given to her at intervals of nine days. After the second injection the dynamometer showed 25°. Appetite and sleep returned and the patient could, unsupported, go across the street, which she had not been able to do for six months. These observations were continued for seven weeks, during which time the patient felt quite well.

OBSERVATIONS OF DR. GOLDBERG AND DR. PANTSCHENKO.
ARTHRITIS DEFORMANS.

Similar results were observed by Dr. Goldberg³⁸⁶ in a patient who had suffered for five years with arthritis deformans, endocarditis ex rheumatismo articularum.

Dr. Pantschenko³⁸⁷ in the same way obtained a cure in a chronic case of arthritis deformans. At the end of the treatment the patient remained for a whole month under medical observation. During the whole time not a single relapse was noticed.

The following undoubtedly merits close attention.

OBSERVATION OF DR. G. V. HIRSCH,³⁸⁸ PHYSICIAN EXTRAORDINARY TO HIS
MAJESTY THE CZAR. ENDARTERITIS OBLITERANS.

Reverend George K., a man of good physique, in his thirty-seventh year began to suffer with affection of the left lower limb. Accompanied by terrible pains, the affection advanced to such an extent that, after dry gangrene had appeared in the big toe, Pirogoff's operation was performed by Professor Wahl. The operation, however, was a disappointment and an amputation below the knee, after Gritti, became necessary. In both cases the wounds healed by first intention. Several months later the same operation, after Gritti, had to be performed also on the right leg, as the endarteritis had caused obliteration of the blood-vessels in a precisely similar manner as in the case of the left leg, until the gangrene, which had set in at the big toe, called loudly for amputation. This was performed by Professor Zoerge von Manteuffel. Three years later in the left forearm the symptoms of endarteritis, which were only too familiar to the patient, appeared in exactly the same manner as it had done in the legs. Here also severe and slowly increasing pains with swelling of the forearm appeared. First the radial and then the ulnar pulse disappeared, while over the swollen dorsal surface of the hand a vicarious pulsation was noticeable. One year later dry gangrene appeared on the fourth and little fingers of the hand, and the pains again increased to such an extent that the patient concluded to submit to another operation. The hour appointed for the operation arrived; "the instruments were in readiness"; at the request of the patient's wife, however, it was postponed.

On the same day the patient for the first time commenced to use *Essentia Spermini-Poehl*. After one month improvement in the condition of the patient

was markedly evident. The pains were much less and ceased entirely in the course of the summer. The gangrenous process was brought to a standstill; the necrotic tissues sloughed off and healthy skin appeared beneath. The nail of the fourth finger, which was attached by a small shred only, had been replaced by one that was perfectly healthy, and firmly attached; the circulation of the blood and the nutrition of the left forearm had wonderfully improved and its previously decreased temperature had risen. Two years later Dr. G. v. Hirsch found that the patient was enjoying good health.

We have already made some theoretical explanations as to the uric acid diathesis, which show that it is connected with the "inactivity" of the Spermin and represents one of the most important forces in the origin of auto-intoxications.

The connection between the decreased intraorganic oxidation and the uric acid diathesis is acknowledged by Klemperer,³⁸⁹ as according to him the unknown "gout-substance" is readily oxidised; all the bodies which operate strongly in oxidising bring it out, while retarded oxidation causes it to concentrate.

It appears from our theoretical explanations that the characteristic symptom of the so-called uric acid diathesis is by no means to be looked for in the deposition of uric acid, but that besides uric acid the xanthin-bodies, etc., take a prominent part in the symptoms of the disease.

The decrease in the alkalinity of the blood and the tissues has already been recognised by Bouchard and E. Pfeiffer as a cause of the deposition of the uric acid in the tissues. This opinion, with which v. Noorden³⁹⁰ does not agree, is, as already said, endorsed by Prof. v. Poehl. He believes that there is no necessity for the assumption of a "special locally active ferment" (v. Noorden).

It is in the chemical diagnosis of the uratic diathesis that the undoubted advantage of the urine-coefficients (the proportions between the single constituents of the urine) over the absolute quantities of any one constituent becomes apparent. E.g., the absolute quantity of uric acid in the urine has nothing characteristic as to the uric acid diathesis. Prof. Poehl, however, in the very great number of analyses of uratics he has made, always found Zerner's coefficient increased, and even in values which were materially higher than 0.4. This uniformity of the coefficient unquestionably indicates that the alkalinity of the textural juices is decreased.

§ 130. Explanation of the therapeutic effects of Sperminum-Poehl in the uric acid diathesis

This phenomenon is in accordance with the decrease in the alkalinity of the blood in chronic articular rheumatism, as has also been established by Lépine,³⁹¹ Canard,³⁹² Jacob, Peiper,³⁹³ and Predtetschensky.³⁹⁴ Peiper (*loc. cit.*) has in arthritis deformans also established a decrease in the alkalinity of the blood. He also recognised in the stagnation and the subsequent deposition of the circulating uric acid the cause of the inflammatory and necrotic phenomena in the loaded tissues. On the other hand, Ebstein has clearly demonstrated that inflammatory and necrotising processes in the tissues are underlying causes of the deposition of the uric acid. These two seemingly opposite opinions do not, in fact, contradict one another, as we have here to deal with a *circulus vitiosus*; the decreased alkalinity in the blood causes a decrease of the textural respiration with accumulation of the products of metabolism (among others uric acid), which operate as foreign bodies or, by toxic influence, interfere with the normal function of the cell, and may also lead the latter to necrosis. If, on the other hand, we have to deal with a local acidulation or an insufficient local supply of blood, that is, an insufficient oxidation, a place in the organism where the reaction is more acid than the circulating juices would, *eo ipso*, produce a precipitation of uric acid. The accumulation of uric acid which now takes place produces an irritation, that is, a further acidulation in the tissue, by which again a further precipitation of uric acid from the circulating juices is induced. Thus the acidulation of the tissues and the deposition of uric acid stand to one another reciprocally as cause as well as consequence.

The increase in the alkalinity of the blood and the simultaneously appearing oxidation of the intermediary products of metabolism would therefore be the most important therapeutic object. This may be obtained by hypodermic injections of *Sperminum-Poehl* as well as by the internal use of *Essentia Spermini-Poehl*.

As already stated, by the use of Spermin the quantity of the urea is relatively increased, while at the same time the quantity of the leucomaines in the urine decreases. In the increased formation of urea Prof. Poehl, with Ruedel, recognises an important factor for the solution, that is, the extraction of the uric acid from the tissues. Here also the practically important

result is obtained that the function of the kidneys now takes place under favourable conditions. In the uratic the appearance of the cylindroids and the hyaline cylinders is a very common phenomenon which Prof. v. Poehl and others would explain by the fact that urine rich in leucomaines causes irritation of the renal tissue.

This fact finds its explanation partly in the more recent experiments on animals made by Gaucher with the introduction of xanthin and hypoxanthin. Gaucher found that after injections of xanthin in animals albuminuria appeared with "nephrite épithéliale." On the introduction of hypoxanthin he also observed albuminuria, the effects being similar to lead or mercury poisoning. Kolisch also very properly compares the uric acid diathesis with lead poisoning. According to Duckworth headaches, hemicrania, ischias, and nervous asthma are early symptoms of the uric acid diathesis.

Beyond doubt the organism frees itself of intermediary products of metabolism (besides others) together with the menstrual blood. In this sense we would explain Hippocrates' words: "Mulier podagra non laborat, nisi ipsa menstrua defecerint."

(2) Sperminum-Poehl in Scurvy.

Observations on the influence of *Sperminum-Poehl* on scurvy have been made by Drs. Shichareff, E. v. Rossi Gretschaninoff, and P. Fleroff among many others.

OBSERVATIONS OF DR. S. SHICHAREFF.³⁹⁵ SCURVY.

Observations on the influence of *Sperminum-Poehl* on scurvy were made by Dr. Shichareff in the summer of 1892 in his hospital at Tscheljabinsk. The large number of the patients, as well as other business, made it impossible for him to keep a record of the cases explicitly in detail. On the other hand, a larger number could not be observed on account of an insufficiency in the supply of *Sperminum-Poehl*. The patients were selected from the large number of the cases of scurvy in the hospital, only the gravest cases being taken. As with the other patients suffering with scurvy, those who were treated with *Sperminum-Poehl* received an antiscorbutic diet and organic acids or their salts. Thus the difference in the course of the disease with or without Spermin became especially apparent. While those who were given *Sperminum Poehl* rapidly improved and left the hospital, those who were otherwise treated, although less seriously affected, while all other conditions were equal, often remained a long time in the hospital.

§ 131. Clinical observations on the therapeutic action of Sperminum-Poehl in scurvy

OBSERVATIONS OF DRs. E. v. ROSSI,³⁹⁶ GRETSCHANINOFF,³⁹⁷ AND FLEROFF.³⁹⁸ SCURVY.

With the above-mentioned results agree also those which were obtained by Drs. v. Rossi, Gretschaninoff, and Fleroff in the Alexander-Semenoff

Military Hospital. All these cases, which in themselves are very interesting, have been explained by the thorough urinalyses made by Prof. Poehl. Unfortunately, however, from lack of space, it is impossible to discuss them here more thoroughly.

§ 132. Explanation of the therapeutic action of *Sperminum-Poehl* in scurvy

As regards the metabolism, and basing our opinion on the analysis, we feel justified in concluding that the scorbutic with the continually decreased Robin-Poehl's coefficient of oxidation shows a proportion of the urea to the chloride of sodium nearly approaching to the normal, thus contrasting the anæmic and the marasmic in whom, as in the course of the acute feverish diseases, the increased quantity of the intermediary products is connected with a simultaneous decrease in the proportion of the urea to the chloride of sodium. The therapeutic effect of *Sperminum-Poehl* in scurvy can therefore be explained on the foundation of the urinalysis as being due to an increase of the intraorganic oxidation.

In the first place, according to v. Jaksch,³⁹⁹ the alkalinity of the blood, which is decreased in scurvy, is brought to the normal. The usual antiscorbutic diet, as well as the treatment with fruit acids which is customary here, leads to the same result, as the acid salts of the organic acids which the fruits contain, are burnt up in the organism to carbonic salts of alkalies. Without exception, the authorities quoted lay stress on the comparatively speedy action of *Sperminum-Poehl* when employed therapeutically in scurvy.

(3) *Sperminum-Poehl* in Diabetes Mellitus.

OBSERVATIONS OF ROSCHTSCHININ.⁴⁰⁰ DIABETES MELLITUS.

§ 133. Clinical observations on the therapeutic effects of *Sperminum-Poehl* in diabetes mellitus

Dr. Roschtschinin reports two cases of diabetes mellitus in which, by the use of *Sperminum-Poehl*, a general increase of the vital forces was obtained, as well as an increase in the energy of the processes of oxidation in the organism. The sugar left the urine in both cases. In one of them even traces of it had disappeared.

OBSERVATION OF PROFESSOR STANGE.⁴⁰¹ DIABETES MELLITUS.

Patient suffered for some three years with a constant thirst, with occasional headaches and sleeplessness. The nervous system was irritable, the disposition changeable. The daily quantity of urine was very great, with a high amount of sugar—5.5 per cent. The treatment advised was: Vichy water with 25 drops of *Essentia Spermini-Poehl*, and the customary diabetic diet. After five days the excruciating thirst which had lasted for three years had altogether disappeared, and the daily quantity of urine was much reduced. At the end of a fortnight sugar was not to be found in the urine, and the patient considered himself as cured. Four months after the cessation of the treatment, although a by-no-means strict attention had been given to

the question of dieting, sugar could no longer be found in the urine. Three months later, however, the condition of the patient grew worse again in consequence of dietary inattention and overwork. Thirst and polyuria reappeared, and the urine contained 3.8 per cent. of sugar. Again a rigid attention to diet, *Essentia Spermini-Poehl*, and Vichy water were prescribed. Immediate improvement followed: the thirst disappeared during the first few days, the urine no longer contained sugar. From then onwards the condition of the patient did not change; nor did sugar again appear in the urine.

Especially interesting in this case is the celerity with which the therapeutic measures (the proper diet, Vichy water and *Spermin*) produced the desired effect. There can be no possible doubt but that such forms of diabetes are curable even without *Spermin*; in the first place by proper dieting. The speedy action here observed, however, especially the disappearance of the thirst, in the early days of the treatment seems to have been caused by the simultaneous use of *Spermin*.

In diabetes, as well as in other cases of glycosuria, the *Spermin* therapy is credited with a series of good results, while in other cases the excretion of sugar, with an otherwise improved general condition, did not seem to be noticeably influenced. Without entering more closely into the manifold theories as to glycosuria, and diabetes especially, together with their relation to the *Spermin* theory, we believe that the action of *Sperminum-Poehl* in those cases of glycosuria which are caused by nervous irritation and acid intoxication (Zuntz, Hoppe-Seyler, Stadelmann, Kraus, Minkowsky, Lépine) is to be attributed mainly to the increase of the intraorganic oxidation.

V. Noorden very properly points out that the decrease in the alkalinity of the blood in diabetes is not caused by loss of bases, but by increase of acid. If in this increase of acid the inorganic acids (SO_4H_2 , PO_4H_3), which come from the animal diet of the diabetic and from disintegrating albumen of the body, take a special part (so v. Noorden), then from *Spermin* an immediate therapeutic effect cannot be expected. When, however, the lower fatty acids—acetacetic acids, lactic acid, beta-oxybutyric acid—take the chief part in this decrease in the alkalinity (as v. Jaksch, Binz, Minkowsky say), *Spermin*, being the ferment of intraorganic oxidation, is directly indicated and the results obtained in diabetes are to

§ 134. Explanation of the therapeutic action of *Sperminum-Poehl* in diabetes mellitus

be explained as brought about by combustion of the organic acids.

III. Diseases of the Nervous System.

(1) Sperminum-Poehl in functional Nervous Diseases (Neurasthenia, Hysteria, Epilepsy, Chorea, Katatony, etc.).

§ 135. Clinical observations on the therapeutic action of Sperminum-Poehl in functional nervous diseases

A considerable number of observations made by different authors, speak as to the beneficent influence of *Sperminum-Poehl* in functional neuroses. Neurasthenia takes the first place; then follow hysteria, epilepsy, and finally chorea. The influence of *Spermin* on the neurasthenic shows itself in the somatic, as well as in the psychical sphere. Sixty-nine cases are described by the following authors: Rostschinin,⁴⁰² Shichareff,⁴⁰³ Bukojemski,⁴⁰⁴ Frétin,⁴⁰⁵ Ostroumoff,⁴⁰⁶ Sokoloff⁴⁰⁷, Podkopajeff,⁴⁰⁸ Krieger,⁴⁰⁹ Goldberg,⁴¹⁰ Postojeff,⁴¹¹ de Buck and de Moor,⁴¹² Sawitsch,⁴¹³ Tuluscheff,⁴¹⁴ Mrotschkowski,⁴¹⁵ Maslennikoff,⁴¹⁶ Schafranoff,⁴¹⁷ Boethlink,⁴¹⁸ Moritz,⁴¹⁹ Snakomzef, ⁴²⁰ Mertwago,⁴²¹ Viktoroff,⁴²² Spiegel,⁴²³ Pantschenko,⁴²⁴ Kondratjef, ⁴²⁵ Finkelstein,⁴²⁶ Nagubnoff,⁴²⁷ Aframowitsch,⁴²⁸ Maximowitsch,⁴²⁹ Tjascheloff,⁴³⁰ Prof. Kostjurin,⁴³¹ G. v. Hirsch, Physician Extraordinary to His Majesty the Czar,⁴³² Prof. Benedict,⁴³⁴ Prof. Ewald,⁴³⁵ Prof. Fuerbringer,⁴³⁶ Prof. Mendel,⁴³⁷ Prof. Krafft-Ebing,⁴³⁸ Dr. M. Salomon.⁴³⁹

By the use of *Sperminum-Poehl* the physical as well as mental weakness disappears. The disturbed function of different systems from the beginning of the treatment with *Spermin* is very soon restored and sometimes even attains to the normal. The patients are enabled to busy themselves for longer continuous periods without feeling tired as formerly, from whence it follows that their work becomes more productive. Neurasthenics lose their involuntary thoughts and show, after the injections of *Spermin* or after the internal use of *Essentia Spermini-Poehl*, a greater confidence in themselves as well as in their surroundings. Disagreeable pains disappear. Sleep improves; the appetite returns and the alimentary canal begins to work more naturally. Nor is *Spermin* without influence on the sexual function in such cases. Besides the above-mentioned favourable results, a considerable improvement in the state of mind of the patient is always observed.

These facts notwithstanding, the question naturally arises whether all the results which are obtained by the treatment of such diseases as are characterised by their irregular course, are fairly to be attributed exclusively to Spermin. When we have to deal with a neurasthenic, the question may well be asked, whether the result obtained has not been produced simply as a result of the physician's suggestion. It is certainly by no means easy to determine how great in each case the influence of this factor may be. Cases are recorded in which a treatment lasting for months and with extremely varying remedies (*e.g.*, the group of the Roborantia and Antinervina, as well as hydro- and electro-therapy with strict directions and diet) was unsuccessful or evinced only a slight improvement. When, however, in such cases as these pronounced improvement follows on the use of *Sperminum-Poehl*, the success can hardly be explained as being attributable to suggestion. If the Spermin results may be thus attributed, equally then might the success of any and all other treatment be so attributed. Why were all these endeavours without influence and good consequences?

In consideration of the large number of reported cases of neurasthenia, we feel obliged to refrain from an extensive discussion of them, and would refer the reader to Prof. A. v. Poehl's book "*Die physiologisch-chemischen Grundlagen der Spermintheorie nebst klinischem Material zur therapeutischen Verwendung des Sperminum-Poehl*," in which the respective cases are reported.

We confine ourselves here to two cases which Dr. Max Salomon reported upon to the Hufeland Society in Berlin.

OBSERVATIONS OF DR. SALOMON.⁴⁴⁰ NEURASTHENIA.

CASE 1.—Patient, female, 48 years old, unmarried, suffered with chronic articular rheumatism, with deposits at the joints of the knees and feet, and with nervousness. In consequence of a severe psychical crisis, caused by family trouble, a grave depression appeared, accompanied by apathy with sleeplessness and loss of appetite. There was considerable emaciation, as well as nightly hallucination. Great sensitiveness of the skin over the chest and stomach was present, so great that the patient groaned aloud upon the least touch. In the urine were many urates, but no albumen. The patient was constipated. Temperature, below the normal = 36.6°. Pulse = 100, small. Bromide of potassium, asafetida, mild narcotic remedies, as well as moral influences, proved entirely unsuccessful. The injections of Spermin, begun on October 29, were made daily, at first at the side of the vertebral column. Save for some altogether insignificant local pains, no other disagreeable

§ 136. Clinical observations on the therapeutic action of Sperminum-Poehl in neurasthenia

symptoms appeared. Local inflammation was never noticed—even the place of injection could hardly be found on the following day. On the first day of the treatment no changes could be seen; nor was the insomnia at all alleviated. After three injections only the sensitiveness of the skin diminished. From that time a continuous improvement commenced in the condition of the patient: by-and-by the apathy disappeared; sleep returned; and the hallucinations disappeared. The appetite improved; the temperature rose to the normal; the pulse became full; the urine clear; the nutrition improved. For a fortnight the injections were made daily, then every second day, and later on at greater intervals. By the end of November the patient had fully recovered: the nutrition was, thanks to the good appetite, excellent; sleep and digestion had become normal. While before the Spermin treatment coagulations frequently appeared in the menses, subsequent thereto the *molimina* were considerably less. The pains in the joints diminished and the mobility increased.

CASE 2.—Patient, female, 54 years old, presented a much more severe case of neurasthenia. Patient had employed vastly varying modes of treatment, finally even electric light had been employed, but without success. Her condition became quite unbearable. She had become utterly anæmic, and visibly emaciated. The muscles were so much weakened that the patient had been for several days unable to rise. At the same time a very pronounced irritation of the optic and auditory spheres took place, and the patient could stand neither light, noise, nor loud talk. She complained of severe clonic cramps in the lower extremities, by which they were thrown high up. Besides this she had severe darting pains in the face, extending even to the scalp. The tongue was much coated; there was complete anorexia. The patient took only small quantities of coffee or tea. Mucous diarrhoea with colic-like pains was present. Temperature = 36.8° ; pulse = 96, weak and soft. Urine very cloudy from urates. No albumen. The patient felt so weak that she prepared herself for an early death. Almost every possible method of treatment was tried, but without success.

In consequence of this aggravation of her condition, injections of Spermin were made daily, along the side of the vertebral column. As the first injections were not attended by any success—not a single symptom improved; the insomnia, of which the patient incessantly complained, remained unchanged—the injections of Spermin were discontinued, and several nervina prescribed, while at night trional also and hypodermic injections of morphine (0.015) were used. When at the end of six days no better results had been obtained with this treatment, Dr. Salomon recommenced the injections of Spermin, but without placing much hope in them. The effects, however, surpassed all expectations. After a few days the patient told him that the cramping pains in the feet had become weaker and rarer; while the darting in the face and the irritation of the sight and hearing begun to subside. The tongue became free; a little appetite appeared; and diarrhoea and colic ceased. In fact, the most excruciating symptom—the sleeplessness, which had remained unchanged for some time—disappeared partially after a fortnight. With the increase of the improvement, Dr. Salomon let the patient stand up—for gradually increasing periods—busy herself with reading, and later with light housework. With proper diet, her weight and strength increased. The injections of *Sperminum-Poehl* were continued every day until the end of December, and later on every second day. In all, fifty injections were made; from time to time they were repeated later, although the disease showed an entirely different course. The patient's frame of mind was quiet and steady;

and she had again taken in hand the management of nearly all her housework. The nutrition was nearly normal; the diarrhœa had ceased; the urine was clear; the temperature and the pulse normal. The sleep alone was not yet entirely satisfactory; she slept, however, every night for shorter or longer periods. In a word, her general condition became a comparatively good one.

One cannot help agreeing with the author that the cases mentioned speak strongly for the favourable influence of *Sperminum-Poehl*. We must endorse the opinion of Dr. Salomon, according to which, for the eventual reputation of the assumption that suggestion had operated in these cases, it may be called to mind that before the treatment with Spermin a long series of the most different remedies had been tried in vain (in the second patient even injections of morphine were of no avail), and that the psychic influence in such a case was also not excluded.

In the discussion of Dr. Salomon's paper the President of the Society, Professor Liebreich, also took part. "The condition of Organotherapy," said he, "was certainly bad, because perfectly pure bodies could not be used. The doctrine of Brown-Séguard, which was very interesting, though a little mystic, at the same time appeared doubtful. To-day, however, we have a considerable number of facts as to Organotherapy which are established beyond doubt and speak for the great significance of this method of treatment. The most important is that now we know the qualities of the remedies employed. The great merit of Professor Poehl is that thanks to his iron energy we have now an efficient remedy—*Spermin*—in a pure condition." Furthermore, Professor Liebreich saw in the observations of Dr. Salomon only another fact speaking strongly in favour of Organotherapy.

The metabolism, always much disturbed in the neurasthenic, is restored to the normal by the action of *Sperminum-Poehl*. This favourable influence appears most strikingly in the results of the urinalyses, as the following case demonstrates.

Patient, female, suffered with neurasthenia, and was at the same time very anæmic. In this case *Sperminum-Poehl sicc. pro clysm.* was employed. The favourable result obtained here was accompanied by the following data in the urinalysis. Robin-Poehl's coefficient, which before the treatment was 100 : 76.37, rose after it to 90.35. The coefficient of the vital energy rose from 100 : 44 to 100 : 57.3. Poehl-Leyden's coefficient rose from 100 : 49.2 to 100 : 67.2. Zerner's coefficient, which had risen before the use of Spermin to 0.80, dropped to 0.42.

Further, Professor Ballet⁴⁴¹ (Paris) recently recommended *Sperminum-Poehl* in neurasthenia. He obtained some remarkable successes. After the treatment with Spermin he gave the ovo-lecithin-billon to strengthen the body.

(a) *Sperminum-Poehl* in Hysteria.

OBSERVATION OF DR. F. BUKOJEMSKY.⁴⁴¹ HYSTERIA.

§ 137. Clinical observations on the therapeutic action of *Sperminum-Poehl* in hysteria

E. P., 43 years old, married, without children, had been ailing for ten years. Patient was of medium size, lean and pale; the adipose tissue spare. A mild case of endometritis; the left ovary painful and a little enlarged. Patient was of a very excitable nature. On the most trifling occasions she became infuriated and cried bitterly. Hyperæsthesia of the optic nerve; strong light, unexpectedly flashing, up caused blepharospasmus; patient was very sensitive to acoustic irritation: the slamming of a door sometimes caused a similar excessive state of excitement. Many areas of the skin surface were of increased sensibility, passing over in sensation of pain, as, for instance, the chest, the abdomen, and the thighs. There were frequent spasms of the bladder, and stranguria. The quantity of the urine was at times diminished. In the first week, during which she was observed on two days only, 400 case ccm. each of urine were passed. Constipation frequent; abdomen bloated. Before and after the menstruation, which was always painful and insufficient, there were abundant leucorrhœa and spells of suffocation with the sensation of the globus hystericus, besides rigour of the upper and lower extremities. Sleeplessness frequently aggravated the above-named symptoms. After four injections of *Sperminum-Poehl*, her frame of mind improved. Patient looked expectantly for company, which before had been a burden to her, so that she finally had anxiously avoided human society. Her general condition improved; her sleep became quieter; and in the morning the patient felt more refreshed. The appetite reappeared after a long time; the bowels moved regularly every second day. After a month the condition of the patient was much improved. None of the above-named symptoms again appeared, and the patient felt perfectly well. Fourteen months after the treatment Dr. Bukojemski received very favourable news from her: "The menstruations have ceased and patient feels perfectly well."

OBSERVATION OF DR. SHICHAREFF. HYSTERIA.

An extremely anæmic person, who had nine or ten hysterical spells daily, and who, for a month, had not been once able to fall asleep without the assistance of a hypnotic, and to whom not one of the means of treatment employed, hypnotism included, had given the slightest relief, was able after two injections of *Sperminum-Poehl* to go to sleep without the use of narcotics. The number of hysterical spells became smaller, and they soon entirely disappeared. The improvement in the condition of the patient was permanent.

OBSERVATIONS OF DRS. MAXIMOWITSCH AND TJASCHELOFF AND PROFESSOR KOSTJURIN. HYSTERIA.

Dr. Maximowitsch⁴⁴⁴ obtained in five cases of hysteria good effects on the general condition; and in two cases of hysteria in soldiers he observed the stimulating action with a favourable influence on the mental state.

Dr. Tjascheloff.⁴⁴⁵ Patient suffered with hysteria gravis. After eight injections of *Spermin*, he noted the non-appearance of the painful hysterical spells during a period of seven months.

Professor Kostjurin.⁴⁴⁶ Patient of 68 years. Hystero-epilepsy. After four injections of *Sperminum-Poehl*, he observed a considerable improvement in the symptoms.

OBSERVATION OF PROFESSOR BENEDIKT⁴⁴⁷ (BERLIN). HYSTERIA.

A highly hysterical lady, who suffered with chronic chorea phonetica, had been for several weeks subject to severe vomiting and anorexia, which went as far as nausea against food. After twelve hypodermic injections of *Sperminum-Poehl*, the patient rapidly improved, and was perfectly cured at the cessation of the treatment.

OBSERVATION OF DR. KONDRATJEFF.⁴⁴⁸ MENTAL OVERWORK.

Patient was exposed to noxious evaporations in the laboratory—anæmia, spitting of blood, constipation. The intraorganic oxidation was materially decreased. On March 5, 1893, the analysis showed the proportion between the total nitrogen in the urine to the urea-nitrogen to be 100 : 87.29. During the treatment with bromide of potassium, it fell to 100 : 83.47. After several injections of Spermin during but five days this proportion rose to 100 : 89.26, and after further use of *Sperminum-Poehl* it reached the normal height, 100 : 95.19. A year before, on February 16, 1892, the urinalysis had shown the proportion 100 : 94.34. Simultaneously with the increase of the processes of oxidation caused by the *Sperminum-Poehl* Dr. Kondratjeff observed a disappearance of the subjective symptoms and of the spitting of blood, together with an improvement in the general conditions.

(b) *Sperminum-Poehl* in Chorea.

OBSERVATION OF DRS. DE BOOK AND DE MOOR.⁴⁴⁹ CHOREA.

Patient V., 10 years old, chorea with prevailing movement in the arms. Bodily strength, poor; blepharitis ciliaris, enlargement of the lymphatic glands. Very pronounced condition of melancholy. Patient cries from the least cause, cannot perform any brain-work; excessively timid. Is the general scapegoat of the other pupils. *Essentia Spermini-Poehl* internally five, later six, then seven drops, three times a day. After from four to five weeks very good results were obtained.

§ 138. Clinical observations on the therapeutic effects of *Sperminum-Poehl* in chorea

(c) *Sperminum-Poehl* in Anæmia cerebri.

OBSERVATION OF DR. HOFMEIER⁴⁵⁰ (BERLIN). ANÆMIA CEREBRI.

Dr. Hofmeier reports some favourable results obtained with *Spermin* in men and women suffering with neurasthenia, tabes, or neuroses from exhaustion. There was a lady of 43 years who was in such declining circumstances in consequence of fibromyoma uteri from her twentieth year that she was condemned to a disconsolate retired life. After all possible means and methods of treatment had been tried more or less unsuccessfully, Dr. Hofmeier subjected her to treatment with injections of Spermin, which gave a surprisingly favourable result. The lady, who could neither walk nor do any kind of work, recovered to such an extent that in a short time she was able to return to social life, could visit theatres and more or less meet all her obligations. From time to time after some hardships the patient returned to Dr. Hofmeier for a repetition of the injections. In this case there was evidently an advanced anæmia cerebri et medullæ spinalis, without any special affection of these organs.

§ 139. Clinical observations on the therapeutic action of *Sperminum-Poehl* in anæmia cerebri

OBSERVATION OF DR. BESPJATOFF.⁴⁵¹ ANÆMIA CEREBRI.

Not long ago also, Dr. Bspjatoff reported a case of very pronounced anæmia cerebri, in which he obtained a complete recovery by treatment with *Sperminum-Poehl*. The disease had lasted fifteen years, and could not be subdued by any means. After the employment of *Sperminum-Poehl*, however, in the form of hypodermic injections, the vomiting ceased almost immediately after the first day of the treatment. The headaches recurred only about twice a week, her appetite returned, her strength increased, and her sleep became normal.

In some forms of epilepsy also *Sperminum-Poehl* has been employed with good results by different practitioners. Especially good results were obtained by Dr. Lion⁴⁵² by a combined method of treatment with *Sperminum-* and *Cerebrinum-Poehl*. To these highly interesting observations we shall return when we discuss the use of *Cerebrin*.

(d) *Sperminum-Poehl* in Katatony.

§ 140. Clinical
observations
on the action
of *Sper-*
minum-Poehl
in a case of
katatony

On the evening of July 23, 1901, an Estlandish woman, 38 years old, was brought into the hospital of the Palace Management of Zarskoje Sselo. She had been in a drowsy condition since July 21. On examination on the 24th, the following was found: pulse, 72, weak, full. Respiration, superficial, 16. Recumbent position, passive. Cataleptic condition not present. Spasmodic twitching of the eye-muscles and the masseters. On forcible opening of the mouth considerable resistance of the lower jaw was found. From time to time the eyes opened in consequence of clonic twitching of the muscles which lifted the eyelids. When the lids were raised the eyeball turned upwards and the pupil could not be seen. The eyeballs made some nystagmic movements in vertical as well as turning directions. The pupils seemed of equal size and reacted well on light. Muscular and tendon-reflexes of the upper extremities were pronounced. The knee-reflexes and those of the Achilles tendon were, especially on the left side, increased, while the skin-, abdomen-, and plantar-reflexes were also stronger on the same side. The throat-reflexes, as well as those of the conjunctiva bulbi, the nose and ears, were entirely absent. The sensation of pain was altogether gone. The inner organs were normal. According to the statements of the relatives the patient had for a week before she fell asleep acted in a very strange manner. She had prayed much, and often sighed; she had been immovable for a longer time, staring at one fixed point. From July 25 to August 3 no change could be noticed in the condition of the patient. Pulse, 78; in the urine traces of albumen. On August 3 the first injections of *Sperminum-Poehl* were made. From August 4 to 21 four ampullæ of *Sperminum-Poehl* were injected daily. On the 10th the first movements were noticed. The patient was observed to flick the flies from her face with her hand. At the same time her appearance improved, and she even commenced to turn herself in the bed. On the 12th, a quarter of an hour after four sinapisms had been applied, she woke up and commenced to talk but with a feeble voice. This, however, seemed to put her to much trouble. She asked for a drink and complained of headache. Later she said that she woke up on July 22 and intended to rise, but had been unable to do so. At first it seemed to her as if every one had died and she alone was alive. With the idea of freeing herself from the anguish and the agonising

thought that all were dead, she fell asleep. However, she heard everything that was going on around her as well as what was said. She also recollected the first visit of the physician, and how she was fed. In the sleep it had seemed to her as if something had fallen on her.

On August 13 both pupils were equally large, reacting well on light. The reflexes of the muscles, as well as the tendons, and those of the knee, heel, and skin were well pronounced. Those of the throat, the conjunctiva bulbi, the nose, and the ears were missing. The senses of taste and temperature were well marked. The sense of pain had everywhere gone (analgesia). The patient spoke much of her three weeks' sleep. Her consciousness was good; the headaches were gone; she only complained of general weakness and weariness. On August 15 the patient stood up. The reflexes of the muscles and tendons were much more lively. On the 17th she no longer felt weak, but her movements were sudden. On the 18th she sat for a long time in the bed in one position; she did not sleep during the night; she prayed incessantly in a low voice. Sometimes she cried aloud, "Jesus," jumped up from the bed, and walked around the room praying. She refused, when others ate; when she was alone, however, she ate two plates of food. On the 20th she did not sleep in the night; she was in a religious ecstasy. On this day she received four tablespoonfuls of bromide of strontium, 4.0 : 180.0. On the 21st she slept well during the night; psychic condition the same. Hallucinations of sight. On the 22nd the injections of Spermin were discontinued and the patient was sent to an asylum.

From the above statements the favourable effects of *Sperminum-Poehl* may readily be seen. We only hint at a few, as, for instance, Robin-Poehl's coefficient of the energy of oxidation, Zuelzer's and v. Eichwald's coefficients, with which we have dealt before (*loc. cit.* p. 141).

(e) *Sperminum-Poehl* in Morbus Basedowii.

OBSERVATION OF DR. FINKELSTEIN.⁴⁵³ MORBUS BASEDOWII.

Patient M. K., female, 27 years old, had ten years ago, and without any apparent cause, some hysteric attacks, together with convulsions of the facial muscles of both sides. In the second year after the beginning of the disease she lost her appetite entirely. She ate practically nothing, often for days and even weeks. The only thing with which she maintained her strength was wine. Towards the end of the second year an enlargement of the thyroid gland and an increased heart-action became noticeable. Simultaneously with the facial convulsions singultus appeared, and later recurred intermittently. The patient became feeble; she was soon tired and slept badly. In the course of these years the patient had been treated by different physicians. She changed the remedies and the climate as often as she did the physicians, looking in vain for deliverance from her troubles. Hypnotism, which was at that time fashionable, was also given a chance. For some time these means seemed effective, but afterwards the condition of the patient invariably became worse again.

As the multiplicity of effort which had been employed in the course of the ten years had proved entirely unsuccessful, injections of *Sperminum-Poehl* were prescribed, to be made twice a week. After a few injections only the spells of singultus became rarer, and the patient slept more quietly. The appetite began to improve; she appeared to take interest in food. The debility decreased. Objectively a considerable decrease of the energy of the contractions of the heart could be noticed. Pulse, 72 to 80. After a month

§ 141. Clinical observations on the therapeutic action of *Sperminum-Poehl* in morbus Basedowii

the convulsions of the muscles of the face and neck had considerably decreased. The spells of singultus had become rarer still. The appetite was altogether satisfactory; the sleep continuously improved and became quite good. The heart-action objectively presented itself within the same limits. The pulse was not more than 72 to 76 a minute. Later the weight increased. Six months later still examination showed that a little enlargement on the right side was all that remained of the goitre. Repeated urinalyses during the whole course of the treatment showed in the beginning a much decreased intensity of the oxidation of the nitrogenous compounds, which often sank to a proportion of 100 : 82.59. After the injections the coefficient of oxidation rose, but always remained below the normal, namely, 100 : 87.42.

§ 142. Explanation of the therapeutic action of Sperminum-Poehl in diseases of the nervous system

From what has been said, it can be seen, and it is also confirmed by the opinions expressed by noted clinicians, which are contained in the literature of the subject, that *Sperminum-Poehl* proves especially useful in functional diseases of the nervous system, especially in neurasthenia. How can all this be explained?

Among the very variable clinical symptoms of neurasthenia the results of the examination of the metabolism is the only one that invariably deviates in the same direction from the physiological rule. In his numerous examinations of the urine of neurasthenics Professor Poehl⁴⁵⁴ always found Robin-Poehl's coefficient decreased, which certainly indicates an accumulation of intermediary products of metabolism in the tissues of the neurasthenic. Differing from the anæmic and those in whom the taking up of oxygen by the lungs is diminished, the relative quantity of the chlorides in proportion to the urea is not always decreased in the neurasthenic. Zerner's coefficient is always increased—above 0.4.

Poehl points out that, by over-irritation, the nervous tissue, as well as the muscular, suffers an acidulation by which the oxidation of the products of the metabolism is more or less checked. This, on its part, leads to very different auto-intoxications of the nervous tissue and is therefore an etiological factor for the appearance of a series of functional neuroses.

Poehl distinguishes between "different kinds of auto-intoxication" of the nervous tissue, as we have here to deal with an overcharging by a series of chemically and physiologically very unequal products of the retrogressive metamorphosis. For instance, neurin is a normal product of the retrogressive metamorphosis of tissues rich in lecithin. Neurin itself is highly toxic (see § 117) with a strong action on the heart. In normal oxidation it is finally changed to non-toxic compounds.

The intermediary products of hydration and oxidation of neurin, however, as, *e.g.*, cholin, are by no means indifferent. Also the xanthin- and the kreatin-groups are represented among the products of the metabolism of the nervous tissue ; and here also we see that the comparatively great toxicity of these compounds decreases only in the higher stages of oxidation. Thus, for instance, according to Landois, kreatin, when applied to the motoric zone of the cortex of the brain, produces convulsions. These few examples might suffice to illustrate some of the auto-intoxications of the nervous tissue with normal products of the metabolism which are only retarded in their oxidation. If the metabolism takes place under the influence of pathogenic microbes or enzymes the factors for the formation of toxic intermediary products of the retrogressive metamorphosis will be much more manifold. The cause of functional neuroses need not always be in toxic products of metabolism, but leucomaines which by themselves are indifferent can do the same, overcharging the nervous system as foreign bodies, that is, as insufficiently oxidised and consequently not readily soluble compounds. *Sperminum-Poehl* is here directly indicated, as it helps to transfer by oxidation the toxic leucomaines into non-toxic ones and the not readily soluble products of metabolism into soluble and diffusible compounds.* At the same time *Sperminum-Poehl* causes the oxidation of the acids (lactic acid, etc., Poehl⁴⁵⁵), which originate through the over-irritation of the nervous system, and the normal alkalinity of the blood is restored.

In 1895 Prof. Dr. Frhr. v. Krafft-Ebing⁴⁵⁶ expressed himself on Spermin therapy in the neurasthenic as follows :

" If Poehl's suppositions are correct, namely, that Spermin acting like a ferment, exercises a considerable influence on the textural respiration, his remedy indeed seems to call upon us to employ it and accomplish something in a neurosis in which defective processes of oxidation or even auto-intoxication ought to have a prominent ætiological and clinical significance, especially in those frequent cases in which uraturia and oxaluria indicate some considerable disturbances of the metabolism."

In the same work Professor v. Krafft-Ebing points out

* It should be remarked that the results of the Spermin therapy are considerably injured by the simultaneous use of alcohol in any form, and sometimes even by bromides.

that Poehl's theoretical views on the nature of neurasthenia (fatigue neurosis) and the action of Spermin in neurasthenics agree with the opinion expressed by Professor P. J. Kowalewsky. He⁴⁵⁷ assumes that in neurasthenia the ganglion-cell is unable to deliver itself by the oxidation of the products of metabolism from their toxic influence and therefore falls a victim to the intoxication.

When describing the results of urinalysis in the neurasthenic Professor Poehl pointed out that in this case the intermediary products of the retrogressive metamorphosis are essentially different from those in anæmia and pulmonary affections, as the former do not accompany a retention of the chlorides. The chemical expression of the fatigue of the nervous system is in its acidulation, which appears in Zerner's coefficient. This coefficient is by Spermin therapy readily lowered in some cases; in others, however, it is extremely slow. This difference is accounted for by the fact that in the cases in which we have to deal with mere fatigue-neurosis, the oxidation that is the destruction of the lactic acid, in the nervous tissue can be accomplished with comparative ease. In those individuals, however, who are at the same time affected with uric acid diathesis or a hereditary taint, the same effect appears but tardily. This latter category of cases has been more thoroughly discussed by Professor O. Lange in his interesting work "Periodical Conditions of Depression and their Pathogenesis on the foundation of Uric Acid Diathesis" (1886). Before this Charcot had recognised the connection between functional neuroses and uratic diathesis, and Dr. R. Vigouroux in his work "Neurasthénie et Arthritisme" (Paris, 1893) has further developed this idea, arriving at the following conclusion: "Tous les neurasthéniques sont des arthritiques, du moins au sens chimique du mot."

The results of a long series of analyses, which Professor Poehl made with the help of Dr. Finkelstein, of the urine of epileptics, demonstrated that the maximum of retention, that is the minimum of excretion of the leucomaines with the urine, immediately precedes the epileptic fit. Therefore this fact seems to point out the accumulation of the leucomaines in the organism as being the direct cause of the fit. This symptom can be used to predict, with a fair degree of certainty, the time of the fit in patients who are affected at long intervals.

By a graphic representation of the excretion of leucomaines with the urine we obtain a slowly-dropping curve which a short time before the fit breaks off, to rise immediately afterwards. The minimum of the excretion of leucomaines occurs about twenty-four hours before the fit. Dr. Krainsky,⁴⁵⁸ in his striking investigation, which he made under the direction of Professor Kowalewsky, has obtained results exactly similar to those of Haig. Both the latter, however, considered only the uric acid. Further, Krainsky made the interesting observation that there seemed to be a certain connection between the diminution of the daily excretion of uric acid and the intensity and frequency of the fits. Usually the maximum of the retention of uric acid amounts during the attack to about 0.25. The greater the retention, so much the stronger attack, according to Klinsky, must be expected. If the retention amounts to more than 0.3, or it does not disappear on the following day, a series of attacks or one very severe attack must be expected. Poehl thinks that epilepsy is produced by certain leucomaines, which accumulate in the organism during the period of retention, and now, with commencing excretion, according to the increase in the leucomaine-curve, spring into motion and pass, with the circulation of the blood, into the substance of the brain in increased quantities. The opinion that this temporary charging of the brain-substance might be capable of producing epileptic attacks is supported by the already-mentioned observations of Gautier on hypoxanthin and xanthin, which produce increase of the reflexes and tetanus. Both leucomaines have been found by Pouchet in increased quantities in the urine of epileptics. Poehl repeatedly observed the same after the attack. Also kreatin and kreatinin, as already stated, produce clonic spasms on application to the motoric zone of the cortex of the brain. Poehl often observed an increased excretion of the kreatin-group after the attack. Rochford⁴⁵⁹ sees in epilepsy the expression of a poisoning with paraxanthin.

If in addition to the favourable results some observers have found an increased frequency in the attacks immediately after the occasional use of Spermin, such a phenomenon is not necessarily opposed to the theory of the action of Spermin, and therefore epilepsy need not be set up as a contraindication to the use of Spermin, as in such cases the increased number of

the attacks is finally followed by a pronounced disencumbering of the tissues.

We know that preparations of bromine interfere with the effects of the Spermin therapy. This can be explained in part by the observations of Rudolf Laudenheimer.⁴⁶⁰ He found that in the beginning bromine accumulates in the organism—only a small part of it is excreted—until what may be called saturation of the body with bromine takes place. From that time on a large excretion of bromine with the urine occurs until the body reaches the bromine-equilibrium. As Nencki has demonstrated that the bromine enters into the chlorine-compounds in the blood and dislodges the chlorine, and the blood therefore becomes poorer in chlorine, Laudenheimer recognises in this the essential cause of bromine-poisoning. We know, however, that the impoverishment of the blood in chlorine accompanies the decrease in the power to transfer oxygen. Consequently by bromine therapy an artificial decrease of the intraorganic oxidation is produced. Therefore the symptomatic action of the bromine-preparations, that is, the postponement of the epileptic fit, is easily accounted for. At the same time, however, it becomes apparent that an influence on the nature of the disease, that is, on the overcharge of the organism with leucomaines, cannot at all be expected from preparations of bromine; but rather a retarded excretion of the products of metabolism.

The bromine therapy produces another noxious effect which injures the organism. The osmotic pressure of the juices, as well as their electric conductivity, are, as Poehl points out, decreased by the bromine therapy. This explains on the one hand the stay of the epileptic fits and on the other the equivalence of the psychic disturbance and depression which so often take place in the bromine therapy. The diminution of the osmotic pressure as well as the electric conductivity is to be explained first by the fact that the atomistic weight of bromine is higher than that of chlorine; and secondly, by the known fact that bromide forms products of substitution, thus decreasing the number of the electrolytes.

The use of cardiac stimulants (adonis vernalis, etc.), which has been advocated by Professor Bechterew⁴⁶¹ for the elimination of the toxic products of the metabolism that are the cause of the epileptic fits, is thus far more rational than the

bromine therapy, because here, instead of the accumulation caused by bromine, an energetic excretion through the kidneys is aimed at.

As we shall see later, Organotherapy furnishes us in cerebrin (cerebrinum-Poehl) with a means which katalytically promotes the second function of the textural respiration, viz., the excretion of the products of metabolism. Thus in addition to the action on the processes of oxidation to which Spermin attends, we have in cerebrin a means of influencing the excretion in a manner likely to increase it.

With Spermin and cerebrin we may combat some eventual auto-intoxications of the nervous tissue. We shall see later that, according to Lion,⁴⁶² Pantschenko,⁴⁶³ cerebrin as well as Spermin has been successfully used in cases of alcoholism. From a theoretical point of view an explanation of this is close at hand, when we consider that Spermin represents the katalysator of the processes of oxidation in the textural respiration, while cerebrin acts as the katalysator of the other function of the textural respiration, that is, the excretion.

(2) Organic Lesions of the Central and Peripheric Nervous System.

(a) Sperminum-Poehl in Tabes dorsalis.

As in the discussion of the part played by *Spermin* in the treatment of organic lesions of the nervous system, we will go back to the observations of Brown-Séquard on the effects of the testicle emulsion. The results that were obtained by the employment of this remedy ought to be attributed to *Spermin* as the active constituent of Brown-Séquard's extract.

§ 143. Clinical observations on the therapeutic action of Sperminum-Poehl in tabes dorsalis

According to Brown-Séquard, up to that time no other method of treatment furnished so many cases of improvement in ataxia as did the injections of his extract. This method of treatment was used in thirty-six cases, in twenty-nine of which either recovery or considerable improvement was obtained. To-day the number of the observations amounts to three hundred and forty-two; good results were obtained in three hundred and fourteen of these cases. To the former observations some new ones may now be added that concern the pure *Spermin*.

A long series of authors (Shichareff, Frélin, Pantschenko, Ostroumoff, Podkopajeff, Werbitski in the

clinics of Prof. L. Popoff, Goldberg, Postojeff, Korsakoff, de Buck, de Moor, Maximowitsch, Prof. Eulenburg, Dr. G. v. Hirsch, Moritz, Sawitsch, Katzauroff, Orlitzki, and others) employed *Sperminum-Poehl* in tabes dorsalis and obtained with it the most favourable results—improvement of the general condition, increase of the muscular strength and the weight of the body, good appetite, and normal function of the rectum and the bladder.

An equally beneficial action of *Sperminum-Poehl* was observed too on the sexual sphere and the nervous system, the pains diminishing or ceasing entirely.

OBSERVATIONS OF DR. MAXIMOWITSCH.⁴⁶⁴ TABES DORSALIS.

In a case of tabes, even after eight injections of *Sperminum-Poehl* the long-lasting and intermittent *crises gastriques* ceased, and did not return for a whole year. The myosis also diminished, but the pupil did not react on light. The knee-reflexes were absent as before. Sleep, however, became normal, and the gait steadier. The sensibility of the muscles and the skin also improved.

It should be added that Dr. Maximowitsch has observed a considerable improvement in several cases after the use of Spermin, while previously all the varying methods of treatment and remedies had proved unsuccessful.

OBSERVATIONS OF DR. M. WERBITSKI.⁴⁶⁵ FROM THE CLINICS OF PROFESSOR L. POPOFF. TABES DORSALIS.

CASE I.—E. S., 60 years old, complained of difficulty in walking, weakness and pains in the legs. A dull, boring pain was felt continually, almost without interruption; further, there were frequently acute lancinating pains in the whole extremity, from the hips to the toes. Sometimes the pain concentrated in the heel, at other times in the knee- and foot-joints. To this were added girdle pains (around the belly) and headaches (forehead, temples, occiput), swelling of the legs, and considerable dyspnœa and cough.

After a three months' treatment with nitrate of silver (0.006 to 0.009 per day), extract nux vomica, and kalium jodatum had proved almost entirely unsuccessful, on the advice of Professor Popoff, *Sperminum-Poehl* was tried in the form of hypodermic injections. After the first injection, as early as the next day, the patient could stand on his feet better and did not throw his legs so high. After the second injection the pains in the hips disappeared, the general feeling improved, and the gait became much more steady. In the lower extremities tactile sensation appeared. The sensibility of the skin and the muscles improved. The pulse became quicker and fuller. After the third injection of Spermin the general condition was excellent. The patient was able to assume certain positions and execute certain movements which he could not previously undertake. The dynamometer showed a considerable increase in his strength. After further injections the condition of the patient visibly improved. Urine was regularly passed; the general condition became good; the sense of location had still further improved under the influence of the last injections. The influence of *Sperminum-Poehl* in the restoration of the sensibility of the skin and muscles appears from the tables which are given in the original.

CASE 2.—After four injections in this case an evident improvement of the tactile sense as well as that of pain at the soles of the feet was noticeable. Previously the soles of the feet had been impervious to pin-pricks. After the fifth injection the patient could stand with closed eyes. After the seventh he opened his right eye wider; after the twelfth his gait became more equal and steady. The sensibility of the skin, that is, the tactile sensation, the sense of location, the electric sensation and that of pain and temperature all improved.

OBSERVATIONS OF DR. G. v. HIRSCH, PHYSICIAN EXTRAORDINARY TO HIS
MAJESTY THE CZAR. TABES DORSALIS.

CASE 1.—Patient, 37 years old, of average build. The pronounced ataxic paraplegia of the lower extremities in which a weakness was noticeable, progressed quickly, and in less than a year it had developed into an ataxic paraplegia. After the patient had first applied to different medical schools, where he was treated with electricity, suspension, hydrotherapy, and different internal medications, but without success, Dr. G. v. Hirsch gave him, as an experiment, some hypodermic injections of *Sperminum-Poehl*. Even after eight or ten injections, one per day, the patient expressed great satisfaction with the treatment. He said he felt subjectively much improved, and he was able to walk in a steadier, more co-ordinated and stronger manner. From these symptoms Dr. G. v. Hirsch was induced to continue the treatment until he had made in all ninety hypodermic injections. Nothing else was used besides *Sperminum-Poehl*. The result was entirely satisfactory. The patient was finally able, not only to walk perfectly free without aid, but also to meet his obligations in the hunting trips of the emperor. The functions of the bowels and bladder returned to the normal and the reflexes, though weak, reappeared.

CASE 2.—In this case, one of ataxic paraplegia of six years standing in a physician 67 years old, Dr. v. Hirsch had occasion to observe the favourable influence of the hypodermic injections of *Sperminum-Poehl* in very severe neuralgic symptoms. Of course, all possible methods of treatment and different waters had been tried, without any success, so that Dr. v. Hirsch found his patient in a perfectly resigned and almost hopeless condition. He complained of severe neuralgic pains in the lower extremities, heaviness of the head, sleeplessness, and a very bad general feeling. Dr. v. Hirsch suggested the hypodermic use of *Sperminum-Poehl*. After about a dozen injections only, but especially after the conclusion of a course of forty injections the patient said as follows: "Of all the different treatments which I have tried in the course of years, none has given me so great a relief as the injections of *Sperminum-Poehl*. The neuralgic pains have abated to such an extent that I have become quite a different man. My head is free; the general feeling is ever so much better than before; I feel stronger on the feet and I can again work mentally. As regards a co-ordinated locomotion, however, no noticeable change has been obtained." About a year and a half later Dr. v. Hirsch satisfied himself that the result obtained by forty injections of Spermin was lasting and the patient was in an excellent mental condition.

OBSERVATIONS OF PROFESSOR EULENBURG⁴⁶⁷ AND DR. THELBERG.⁴⁶⁸
TABES DORSALIS.

Professor Eulenburg in a very severe case of tabes dorsalis observed a very pronounced stimulating action of *Sperminum-Poehl*,

Dr. Thelberg also observed some good results in a case of tabes after hypodermic injections of *Sperminum-Poehl*. Patient, 40 years old, had thirteen years previously suffered with syphilis, and was a year before affected with tabes. The characteristic symptoms had already appeared in the face. Various means (inunctions with blue ointment, iodide of potassium, arsenic, tub-baths, rest) were employed, but unsuccessfully. Then, simply as an experiment, the patient was subjected to treatment with *Sperminum-Poehl*. At first an injection of 1 ccm. of Spermin was made every day. After six injections the pains in the bladder and the rectum ceased, and the general feeling improved. After the twelfth injection the passing of the urine became perfectly normal, and the gait much more steady.

1 OBSERVATION OF DR. JACOBY.⁴⁶⁹ TABES DORSALIS.

Dr. Jacoby reports a case of tabes in which, after many different methods of treatment (including electrotherapy) had been employed and had proved altogether unsuccessful, the therapeutic action of *Sperminum-Poehl pro injectione* was quite pronounced.

Patient, 30 years old, contracted, late in 1897, an ulcer durum and condylomata lata ad anum. In the beginning of 1898 he made thirty inunctions of blue ointment. * Early in 1901 he developed some papules on the mucous membrane of the throat and several months later some extended secondary symptoms which disappeared after thirty-six inunctions a 4.0. Two years later the first tabetic symptoms appeared: increasing stiffness in the legs, excruciating pains in the knees when walking, disturbed sleep, interrupted by frequent twitchings. The knee-reflexes disappeared and the gait became unsteady and irregular—pronounced ataxia. The muscular sensation in the legs was entirely gone. To this were added incontinence of the urine and decrease of the sensibility of the lower extremities, debility, tiredness, impotency, finally perfect incapability to walk. Thirteen injections with vasogen-mercury, which were used against these symptoms, were unsuccessful, as were galvanisation, faradisation, and gymnastics. After these failures Dr. Jacoby tried hypodermic injections of *Sperminum-Poehl*. In the first week two injections were made every day, in the next week one per day, and then one every second day. After the first ten injections the following changes appeared: increased strength, quietness in the sleep, and discontinuance of the incontinence of the urine. The debility and lassitude in the whole body, the stiffness and the unsteadiness in the legs, disappeared. The disturbances of the co-ordination were gone, the muscular sensations had returned, the sensibility had improved. The right pupil again reacted, though feebly, on light. The sexual instinct, which seemed entirely gone, had become quite noticeable.

Dr. Jacoby accounts for the extremely favourable effects of *Sperminum-Poehl* by the fact that it removed from the organism toxins of which some have a paralysing, others an irritating, influence on the nervous system.

From a urosemiotic point of view tabes very frequently shows a symptom common to many diseases: namely, a lowering of Robin-Poehl's coefficient of oxidation. Here, however, in contradistinction to the anæmic and marasmic, the proportion of urea to chloride of sodium is scarcely at all

§ 144. Explanation of the therapeutic action of *Sperminum-Poehl* in tabes dorsalis

changed. The decrease in the intraorganic oxidation after separation of the spinal cord had been already demonstrated by Quingnaud. (On the action of *Sperminum-Poehl* which Prof. Prince Tarchanoff has observed in animals with severed spinal cord *see* §§ 94 and 95.)

From this standpoint the favourable influence of the Spermin therapy often observed on certain symptoms of tabes can be satisfactorily explained.

We cannot refrain from mentioning that some authors who have obtained good results with *Sperminum-Poehl* in tabes, look to "suggestion" as the cause—*e.g.*, Motschutkowsky, Ewald, etc.

If these observers had made systematic urinalyses, they would have convinced themselves that the metabolism of the tabetic is favourably influenced by the use of Spermin. This is a symptom which is altogether independent of suggestion.

Poehl justly points out that in the tabetic the urine mostly contains an increased amount of paired sulphuric acids, which points to an increased putrefaction in the bowels. *Sperminum-Poehl* has no influence on this source of auto-intoxication; hence also a series of bowel-symptoms in tabes are not influenced by the Spermin therapy. In any case it is the duty of the physician to remove the auto-intoxication from the bowels by proper means employed simultaneously with or before the Spermin.

In the discussion of the results obtained by the Spermin therapy in neurasthenia and other forms of disease based on excessive irritation and over fatigue, the action of *Sperminum-Poehl* has been sufficiently explained. Whether, according to Edinger, Helbing, Schulze and others, over-irritation and over-fatigue play an essential part in the ætiology of tabes, or whether we have here in the first place to deal with an auto-intoxication from syphilis (Erb v. Krafft-Ebing), still there is certainly a decreased intraorganic oxidation with all its consequences, and therefore theoretically the employment of *Sperminum-Poehl* is correct.

Werbitski in the clinics of Prof. L. Popoff,⁴⁷⁰ Physician Extraordinary to his Majesty the Czar, has observed an improvement in the sensibility of the skin of the tabetic (sensation of location, electric cutaneous sensibility, etc.), which has not only a practical but also a theoretical interest. Poehl

has already pointed out that the decrease in the cutaneous sensibility is to be considered as brought about by a kind of auto-intoxication.

Compounds like cocain, eucain, etc., as is known, produce a local anæsthesia. Poehl had occasion to observe in seventeen cases after the hypodermic or internal introduction of cocain a considerable decrease in the alkalinity of the blood, that is, an increased discharge of acid with the urine.

Adrenal which, as mentioned before, operates diametrically opposite to Spermin, also produces anæsthesia; and in combination with cocain and eucain small fragments of a milligramme of cocain as well as of adrenal, are sufficient for the production of anæsthesia.

We have besides direct observations which demonstrate that in intoxication with cocain some injections of *Sperminum-Poehl* have a favourable influence on the decrease in the alkalinity of the blood as well as the so-called cocain-intoxication.

From all this we see that not only is the general auto-intoxication which is peculiar to the tabetic favourably influenced by *Sperminum-Poehl*, but so also are the local symptoms of auto-intoxication, as far as they are caused by decreased textural respiration. The more recent observations of Dr. Maximowitsch⁴⁷¹ on the favourable influence of *Sperminum-Poehl* (especially in the form of *Essentia-Spermini-Poehl*) on arteriosclerosis corroborate the latter fact. That the decrease of the textural respiration in arteriosclerosis really plays an important part is shown by the recent experiments of Dr. Walter Erb.⁴⁷² They prove that in animals adrenal, which physiologically operates as a katalysator of the processes of reduction in antagonism to Spermin, produces arteriosclerosis.

(b) *Sperminum-Poehl* in Hemiplegia, Paralysis, Myelitis, etc.

§ 145. Clinical observations on the therapeutic action of *Sperminum-Poehl* in hemiplegia, paralysis, myelitis, etc.

The stimulating and dynamogenic action of *Sperminum-Poehl* has also been observed in other nervous diseases which are characterised by organic lesions of the nervous system. (Roschtschinin,⁴⁷³ Shichareff,⁴⁷⁴ Krieger,⁴⁷⁵ Goldberg,⁴⁷⁶ Sokoloff,⁴⁷⁷ de Buck and de Moor,⁴⁷⁸ Nagubnoff,⁴⁷⁹ Wichert,⁴⁸⁰ Maximowitsch,⁴⁸¹ Mrotschkowski,⁴⁸² Vik-

toroff,⁴⁸³ Frétin,⁴⁸⁴ Ulrich,⁴⁸⁵ Katzauroff,⁴⁸⁶ Belilowsky,⁴⁸⁷ Prof. Belljarminoff,⁴⁸⁸ Jakowleff,⁴⁸⁹ Deloff, Sergijeff,⁴⁹⁰ and others.) We will confine ourselves to the discussion of some illustrative cases from the large number of these observations

OBSERVATIONS OF DR. ROSCHTSCHININ,⁴⁹¹ THROMBOSIS ARTERIÆ FOSSÆ SYLVII. HEMIPLEGIA.

CASE 1.—Manufacturer M., 70 years old. Symptoms of paralysis nervi facialis dextri. Paralysis of both extremities of the same side, and aphasia. From the course of the disease a thrombosis of the arteria fossæ Sylvii could be diagnosed with great probability. After several injections of *Sperminum-Poehl* Dr. Roschtschinin found a rapid improvement.

CASE 2.—In Lieutenant-General B., after an apoplectic stroke, paralysis of the upper and paresis of the lower left extremity (hemiplegia) appeared. Tonic spasm of the left arm was present; the contracture of the hand was so strong that the finger-nails were firmly pressed against the volar surface. The least attempt at separating the fingers was painful. This condition lasted about two years. Patient showed obesity and there was somnolence. The appetite was satisfactory. The arteries were slightly sclerotic. There was catarrh of the bladder, and therefore constant strangury. Increase of the reflexes in the lower extremity. With the increase of the number of the injections of *Sperminum-Poehl* the tonic spasm of the muscles of the left arm, as well as the contracture of the left hand, became weaker. Noticeable was the improvement of the frame of mind and the general condition. The strangury recurred less frequently. Supported by a cane the patient walked more easily around the room.

CASE 3.—Quite recently Dr. Roschtschinin reported the splendid results he obtained in a case of hemiplegia: After sixteen injections of *Sperminum Poehl* the patient commenced to walk unsupported and without cane.

For the understanding of the action of *Sperminum-Poehl* in this and in similar cases we give the following explanation.

The paralysis is brought about by some disturbance of the normal function of the nervous system. This disturbance is produced by hæmorrhages which destroy a part of the nervous substance. Besides, the products of the disintegration of the blood may produce a local neurosis followed by acidosis of the particular part of the nervous substance.

In all probability in these cases the alkalinity of the tissues is increased by the influence of *Sperminum-Poehl*, and the processes of oxidation are increased. The accumulated products of disintegration, which as foreign bodies disturb the tissues in their functions, are changed to soluble compounds; they are excreted from the affected parts and pass over into the circulation. In this way the disappearance of the paralysis by the removal of the ætiological factors which cause a disturb-

§ 146. Explanation of the therapeutic action of *Sperminum-Poehl* in paralysis

ance of the normal function of the brain substance is explained.

OBSERVATION OF DR. CARL SCHULIN⁴⁹² (BILLINGS, MONT. U.S.A.).
PARALYSIS.

Patient, an elderly lady, suffered with partial paralysis of the left side of the body. The urinalyses showed a considerable deviation from the normal. The coefficient of oxidation was as low as 80. After five days treatment with *Sperminum-Poehl* (three injections daily), the coefficient of oxidation was up to 89.472. The general condition of the patient improved visibly, although the paralysis itself could not be cured. Two months after the treatment with *Sperminum-Poehl* the coefficient of oxidation was down to 84. The paralysis showed no improvement; the general condition of the patient, however, was very good.

OBSERVATION OF DR. SHICHAREFF,⁴⁹³ MYELITIS.

Patient, 53 years old, extremely emaciated, looking disheartened. Myelitis of the lumbar part of the spinal cord. The legs were very weak; patient walked with much difficulty and could hardly go upstairs. Irregular action of the bladder, obstinate constipation. A series of nine injections of *Sperminum-Poehl* produced a considerable improvement of his condition. The pathological symptoms were removed in the following order: first appeared an improvement of the feet, which at the end of the treatment had become so strong that the patient could not only go upstairs quickly, but he was able to bend his knees several times in quick succession, and could even without assistance mount a horse; thereafter the function of the bladder, and finally that of the intestinal canal, was restored.

OBSERVATION OF DR. KRIEGER,⁴⁹⁴ MYELITIS CHRONICA.

Patient, 57 years old, complained of increasing weakness, first in the right, then in the left leg, as well as a sensation of heaviness in the legs; later spells of dizziness were added. Patient submitted to medical treatment, but in vain. The weakness of the legs increased; patient could no longer walk; was easily excited, and suffered from sleeplessness; the spells of dizziness increased.

The treatment with *Sperminum-Poehl* yielded the following results: after five injections patient could rise from the armchair and stand without faltering with heels and toes close together. After fifteen injections he walked quite firmly and could even go upstairs. Patient felt much strengthened and slept well during the night. No other medicine than *Sperminum-Poehl* was used.

OBSERVATION OF DR. SOKOLOFF,⁵⁹⁵ POLIOMYELITIS ACUTA ANTERIOR.

Officer, 54 years old. Paralytic symptoms in both legs with noticeable atrophy of the respective muscles. The cutaneous sensibility was in these places preserved; the reflexes, however, of the skin as well as the tendons failed. We had therefore to deal with an inflammation of the anterior horns of the grey matter of the spinal cord (poliomyelitis acuta anterior adultorum). The treatment with tonics, local derivation, later on galvanisation of the spinal cord and faradisation of the paralysed muscles, was for a month entirely unsuccessful. The paralysis remained, as before, total, and the atrophy of the muscles progressed so that finally at the end of the period named the muscles of the lower part of the leg were hardly perceivable as more than strings.

To this were added loss of appetite, general emaciation, and debility. The patient, on account of his weakness, remained mostly in bed, and could sit up for a short time only. In consideration of his extremely sad condition Dr. Sokoloff, as the ordinary means did not suffice, determined to try a new stimulating tonic, viz., *Sperminum-Poehl*, administered hypodermically. To his great surprise, within twenty-four hours after the first injection the patient commenced to move his legs considerably. All other methods of treatment were discontinued and a second injection was made, with the result that the general condition and the appetite improved, and the mobility of the legs increased to such an extent that four days after the first injection the patient could rise and stand on his feet. With the third injection—six days after the first—Dr. Sokoloff terminated the treatment, as the patient could move around the room freely, felt well, had a good appetite and rapidly increased in weight.

OBSERVATIONS OF DR. SCHULIN⁴⁹⁶ (BILLINGS, MONT. U.S.A.).

PROGRESSIVE MUSCULAR ATROPHY.

Dr. Carl Schulin observed in a long series of cases of the most variant affections of the nervous system a decrease in the coefficient of oxidation, which visibly rose under the influence of injections of *Sperminum-Poehl*. Of special interest was the following case of progressive muscular atrophy.

Patient, P. S., married, father of three healthy children (there was no syphilis), had been suffering for two years with progressive muscular atrophy. It was well pronounced in the upper as well as the lower extremities so that the patient could with difficulty write and walk. The feet were stiff. The general condition was still fairly good. On January 15, 1900, his weight was 135 pounds. The urinalysis gave the following result: Specific gravity, 1.016; reaction acid; traces of albumen; urea, 40.5; coefficient of oxidation, 77.33 : 100. Every day for a fortnight one ampulla of *Sperminum-Poehl* was injected. On January 31 the urinalysis showed: Specific gravity, 1.023; urea, 24.0; coefficient of oxidation, 83 : 100; weight, 131 pounds. The general condition was good; and was better than before. The physical strength was not diminished. The injections of Spermin were now discontinued. The urinalysis made on February 15 gave the following result: Specific gravity 1.019; reaction acid; urea, 22; no sugar and no albumen; coefficient of oxidation, 94 : 100; weight, 132½ pounds. General condition good. On February 15 and 16 two injections were made each day. The urinalysis made on February 18 gave the following result: Specific gravity, 1.013; reaction acid; urea, 18.6; no sugar or albumen; coefficient of oxidation, 90.75 : 100. On March 15 again a urinalysis was made with the following result: Specific gravity, 1.020; reaction acid; no sugar or albumen; coefficient of oxidation, 86 : 100. Weight, 132½ pounds. The general condition was very good; the strength of the muscles of the shoulder, however, had become less.

IV. Employment of *Sperminum-Poehl* in Ophthalmology.

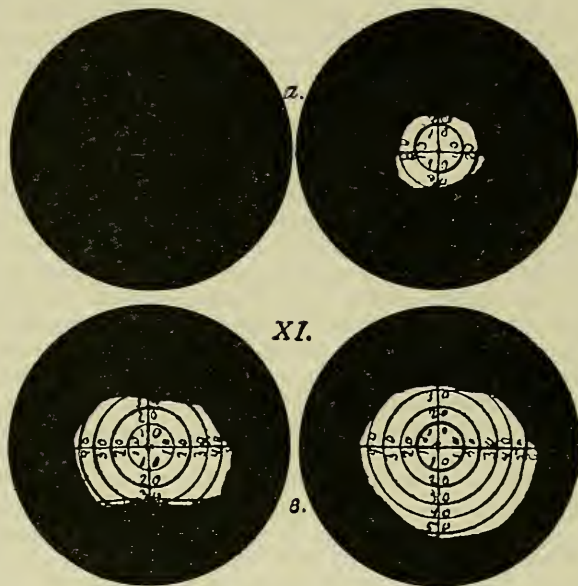
(Atrophia Nervi optici, etc.)

Of late *Sperminum-Poehl* has also been used in another branch of medicine, namely in ophthalmology. Relative thereto we have, besides others, a special article by

§ 147. Clinical observations on the therapeutic action

of *Sperminum-Poehl* in atrophy of the optic nerve, etc.

Dr. Jakoleff, from the eye-infirmiry of Professor Belljarminon. According to him several oculists have employed *Sperminum-Poehl* with remarkable success in the treatment of eye diseases, especially in affections of the optic nerve; sometimes also the retina. For instance, Dr. Kazauoff used *Sperminum-Poehl* with success in a case of atrophy of the optic nerve, paralysis of the accommodation, and tobacco-poisoning. Further, Dr. Belilowsky⁴⁹⁷ used it in two cases and



ATROPHY OF THE OPTIC NERVE.

(a) Before the treatment $\begin{cases} \text{V.d.} = 2/\text{cc.} \\ \text{V.s.} = 1/1000. \end{cases}$

(b) After twelve injections of *Sperminum-Poehl* $\begin{cases} \text{V.d.} = 18/\text{cc.} \\ \text{V.s.} = 2/\text{cc.} \end{cases}$

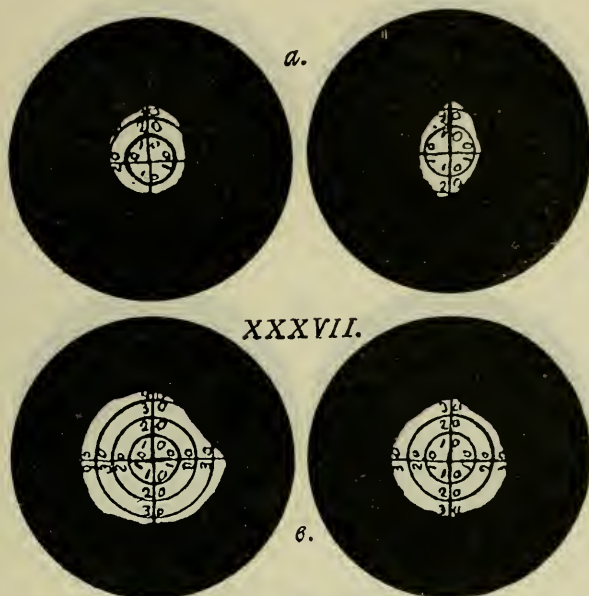
Dr. Sergieff⁴⁹⁸ in several cases of atrophy of the optic nerve with distinct success. Dr. Jakowleff made it a special object to discover what results can be obtained by the use of *Sperminum-Poehl* in ophthalmology.

OBSERVATIONS OF DR. JAKOWLEFF⁴⁹⁹. ATROPHY OF THE OPTIC NERVE.

Basing his judgment on one hundred and one observations made in the eye infirmiry of Professor Belljarminoff, Jakowleff reaches the following conclusions for the indications of Spermin therapy in eye diseases:

(1) In nearly all (forty-four) cases of atrophy of the optic nerve (excepting those in which the vision was =0), after the use of *Sperminum-Poehl* an improvement of the vision was observed; in some cases an even quite considerable one. In one case—patient 40 years old, vomited blood—before the injections of Spermin V.R. $\frac{12}{200}$, V.L. $\frac{1}{\infty}$; after sixteen injections V.R.

$\frac{20}{200}$, V.L. $\frac{5}{1000}$; the field of vision enlarged. In another case—patient of 62 years, just recovered from typhoid fever—before the injections of



ATROPHY OF THE OPTIC NERVE.

(a) Before the treatment $\left\{ \begin{array}{l} \text{V.d.} = 20/\text{xxx.} \\ \text{V.s.} = 20/\text{xx.} \end{array} \right.$

(b) After seven injections of Sperminum-Poehl $\left\{ \begin{array}{l} \text{V.d.} = 20/\text{xx.} \\ \text{V.s.} = 20/\text{xx.} \end{array} \right.$

Spermin V.R. $\frac{2}{200}$, V.L. $\frac{1}{1000}$; after twelve injections: V.R. $\frac{18}{200}$; V.L. $\frac{2}{200}$.

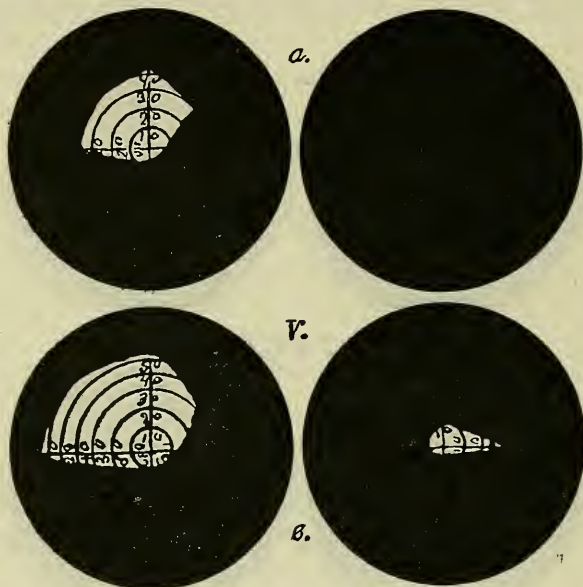
Enlargement of the field of vision. In a third case—36 year-old patient (syphilis ?) before the injections of Spermin: V. of both eyes = $\frac{2}{200}$; very

narrow field of vision; after the injection V. of both eyes $\frac{20}{15}$; enlargement of the field of vision.

(2) In opacities of the vitreous body (thirteen cases) the opacity, according to the ætiological moment, disappeared altogether or but temporarily. In a patient of 40 years, before the injections: considerable diffuse opacity; floating flakes in large numbers; V.R. $\frac{20}{40}$; after six injections: the diffuse

opacity disappeared, floating flakes in smaller quantity, V.R. $\frac{20}{20}$; V.L. $\frac{20}{20}$. In another case—patient of 41 years, highly myopic—before the injections: V.R. $\frac{20}{70}$; V.L. $\frac{1}{1000}$; opacity of the vitreous body; after six injections: V.R. $\frac{20}{40}$; V.L. $\frac{10}{100}$; the opacity disappeared; the field of vision enlarged.

(3) In two cases of amblyopia alcoholica the vision reached the normal again after the use of Spermin.



ATROPHY OF THE OPTIC NERVE.

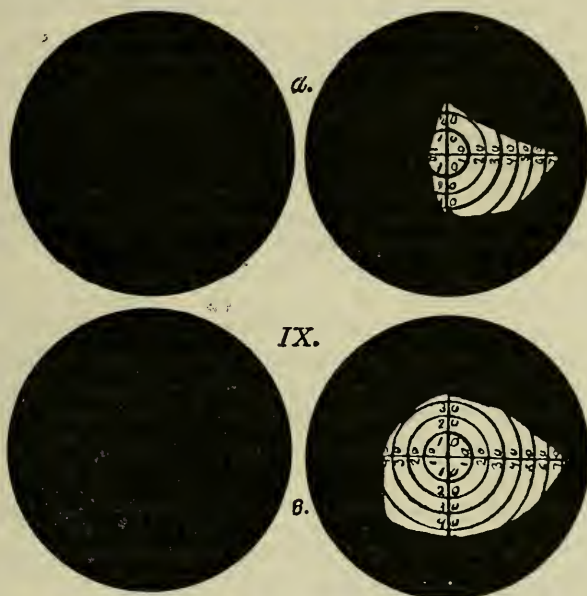
(a) Before the treatment $\left\{ \begin{array}{l} \text{V.d.} = 12/00. \\ \text{V.s.} = 1/\infty. \end{array} \right.$

(b) After sixteen injections of Sperminum-Poehl $\left\{ \begin{array}{l} \text{V.d.} = 20/cc. \\ \text{V.s.} = 5/1000. \end{array} \right.$

(4) In neuritis, neuro-retinitis, choroiditis disseminata, and retinitis pigmentosa *Sperminum-Poehl*, although in most cases without influence on the course of the disease itself often improved the vision. Patient of 35 years—neuritis optica in left eye—before the injections V.L. $\frac{20}{70}$, the disc protruding, abnormally enlarged, with very indistinct outlines. After six injections: V.L. $\frac{20}{20}$; outlines of the disc more distinct; opacity disappeared. Patient of 28 years—choroiditis disseminata in both eyes, diffuse opacity of the vitreous body in the right eye; ecchymoses of traumatic origin in the left vitreous body; before the injections: V.R. $\frac{20}{200}$; V.L. $\frac{1}{\infty}$; after thirty injections: V.R. $\frac{20}{70}$; V.L. $\frac{10}{200}$; the opacity of the right vitreous body disappeared; the ecchymoses in the left nearly entirely reabsorbed.

(5) In ulcerative keratitis subconjunctival injections of Spermin should be tried, because in some cases the further spreading of the process has been stopped in this way.

(6) *Sperminum-Poehl* increases for a short time the strength of the ciliary muscle. In one case—patient of 40 years—hypermetropia and presbyopia—the Sunctum proximum was before the injections of Spermin for both eyes with $+2.50$ D. = $9''$; after the injections the punctum proximum was with the same lenses removed from $9''$ to $7''$, while the range of accommodation rose for both eyes from 3.75 D. to 5.0 D.



ATROPHY OF THE OPTIC NERVE.

(a) Before the treatment $\begin{cases} \text{V.d.} = 20/\text{lx.} \\ \text{V.s.} = 1/\infty \end{cases}$

(b) After ten injections of *Sperminum-Poehl* $\begin{cases} \text{V.d.} = 20/\text{xl.} \\ \text{V.s.} = 1/\infty \end{cases}$

As touching the above-mentioned observations of Dr. Jakowleff, *Sperminum-Poehl*, in the opinion of Professor Poehl, has an undeniable influence on the osmotic qualities of the juices of the body and their alkalinity. In this way also the beneficial influence of Spermin in cases of atrophy of the optic nerve is to be explained.

OBSERVATIONS OF DR. SNEGIREFF⁵⁰⁰. ATROPHY OF THE OPTIC NERVE.

The conclusions reached by Sniegireff do not altogether agree with the results obtained by Jakowleff. In the Alexander Eye Infirmary in Moscow he treated twenty-seven cases

of atrophy of the optic nerve with *Sperminum-Poehl* and found the following :

(1) From injections of *Sperminum-Poehl* in cases of atrophy of the optic nerves, in from 25 to 43 per cent. of the cases an improvement of the vision may be expected. A more or less essential improvement of practical importance and exempt from errors of investigation can be obtained in about one half of the cases. In the other cases the vision does not improve and may become sensibly worse. (2) Essential results (0.1 and more) can be expected only in those cases in which there still exists a comparatively good vision (about 0.5). (3) What has been said concerning the vision applies also to changes of the field of vision, although a direct relation between both factors has not been observed. (4) To judge from the favourable results, the number of injections required amounts to about from twelve to twenty. (5) It appears, therefore, that *Sperminum-Poehl* should be ranked with those means which are to be employed in cases of atrophy of the optic nerves.

The same author observed the disappearance of paresis of accommodation in a tabetic and in a healthy man who had a fortnight previously passed through an attack of diphtheritic angina.

OBSERVATIONS OF DR. A. LOMAKIN.⁵⁰¹ ATROPHY OF THE OPTIC NERVE.

Dr. Lomakin treated three patients with *Sperminum-Poehl*. In two cases there was atrophy of the optic nerve, which was undoubtedly relieved by the use of Spermin. In one case the vision was improved and the field of vision enlarged. Before the treatment the vision was : R.E. $\frac{1.25}{200}$, L.E. $\frac{2.5}{200}$; after twelve injections of *Sperminum-Poehl* : V.R. $\frac{3}{200}$; V.L. $\frac{6}{200}$. Later on some injections of strychnia were also made (sol. strychnini nitrici one per cent.), and the following result was obtained : V.R. $\frac{4}{200}$; V.L. $\frac{10}{200}$.

In the third case (effusion into the left vitreous body) the vision before the treatment was less than $\frac{1}{200}$; with correction by + 10.0 D. spherr., it was $\frac{15}{200}$. After eight injections of *Sperminum-Poehl* the vision was $\frac{3}{200}$, and with the above-named correction $\frac{20}{200}$. Before the treatment nearly the whole field of vision was full of flakes and dark-grey stripes, so that the fundus was hardly visible. After the treatment the haziness was reabsorbed so that the disc, as well as the blood-vessels of the retina (which were before invisible) could clearly be seen. Then there were made a further ten subconjunctival injections of a two-per-cent. solution of chloride of sodium. These, however, did not yield any result. Patient was for about two and a half weeks more under medical observation. During this time there was no progress in the disease : impairment of the vision could be noticed. It can be safely assumed that there was no further progress, as the patient lived in the same town and if he had noticed any impairment of his condition would doubtless have applied to the physician. Dr. Lomakin concludes from his cases that, thanks to the Spermin treatment, the first of his patients could resume her domestic occupa-

tions, without being a burden to herself and her folks, and was in all probability saved from total blindness.

OBSERVATION OF DR. CARL SCHULIN.⁵⁰² ASTHENOPIA AND NYSTAGMUS.

In a case of asthenopia with nystagmus in a boy of ten years, Dr. Carl Schulin observed a lowering of the coefficient of oxidation to 83. After a few weeks of treatment with *Essentia Spermini-Poehl* the coefficient rose to 88. The general condition was much improved and the eyes were more quiet. Later on the boy spent three months in the country in open air, and returned sound and with a quiet look.

OBSERVATION OF DR. BOSSE.⁵⁰³ ATROPHY OF THE OPTIC NERVE.

Dr. Bosse observed a case of atrophy of the optic nerve in a tabetic in which the vision constantly grew worse. Even at the beginning of the treatment with *Sperminum-Poehl* a check was placed on the progress of the disease, which was followed by a noticeable improvement. The lancinating pains in the extremities ceased.

V. Diseases of the Heart, the Lungs, and the Kidneys.

Sperminum-Poehl in Weakness of the Heart from Affections of the Heart and Lungs.

Medical literature furnishes a very large number of observations on the employment of *Sperminum-Poehl* in the above-named group of diseases (*e.g.*, Roschtschinin, Filipps, Zakrjewski, Finkelstein, Nagubnoff, v. Hirsch, Boethlingk, Klimontowitsch, Prof. Kostjurin, Huebbenet, Schafranoff, Shichareff, Injasewski, Mrotschkowski, Nikolski, Sokoloff, as well as others). We shall confine ourselves here to a short discussion of a few of these observations.

§ 148. Clinical observations on the therapeutic action of *Sperminum-Poehl* in weakness of the heart from affections of the heart and lungs

OBSERVATION OF DR. ZAKRJEWSKI.⁵⁰⁴ WEAKNESS OF THE HEART AFTER SEVERE DIPHTHERIA.

In a case of severe diphtheria in an eleven-year-old girl, on the twelfth day of the disease the general condition became worse, notwithstanding the appearance of a local improvement. The pulse-wave sank; arrhythmia appeared; fainting spells were prevalent. One ccm. *Sperminum-Poehl* was injected. Within half an hour the pulse became more regular and full, and the general condition improved. On the following day a second injection was made, after which the pulse became perfectly normal. A similar spell, aggravated by very painful precordial anxiety and extremely alarming general symptoms, re-appeared a week later. Again *Sperminum-Poehl* was injected, and was again followed by considerable improvement, and this more speedily than after the first injection, *viz.*, a bare ten minutes after the injection. The favourable influence of the injections of Spermin showed itself repeatedly and the author succeeded in preventing the outbreak of these spells by making the injections immediately on the appearance of the prodromic symptoms.

The favourable results obtained induced Dr. Zakrjewski to make injections of Spermin on several consecutive days with the result that the spells entirely ceased and the patient recovered.

OBSERVATION OF DR. KLIMANTOWITSCH.⁵⁰⁵ DEBILITY AFTER A SEVERE CASE OF TYPHOID FEVER.

A nineteen-year-old patient of Dr. Klimantowitsch was, after a severe attack of typhoid fever, seized with a condition of debility in which he remained for about three weeks. Temperature from 36° to 36.5° ; pulse, 56 to 54, filiform; aphasia. Paretic condition of the extremities; trembling of the head; disturbance of the sphincter muscles (of the bladder and the rectum)—such was the condition of the patient before Spermin was employed. After the first injection of *Sperminum-Poehl* the pulse became fuller and rose to 66–68; while the temperature went up to 37.5° . After some further injections the other symptoms of debility also disappeared.

The effects of the *Sperminum-Poehl* in these cases are so great that when reading of them we ask almost involuntarily whether the improvement cannot be explained as being brought about by the natural course of the disease. Without denying all the influence of this factor on the course of the disease, we need only point to the results obtained with Spermin in similar cases (see the case of Dr. Hiltebrandt) in order to establish the fact that there, as here, *Sperminum-Poehl* is capable of exercising a dynamogenic influence on the organism.

OBSERVATION OF DR. NAGUBNOFF.⁵⁰⁶ VITIIUM CORDIS ORGANICUM ET ARTERIOSCLEROSIS.

Patient, M. B., female, 75 years old, complained of dyspnœa, cough, feebleness, pains in the side and in the pit of the heart; she could not walk. The examination showed that the heart was enlarged; some sounds at the auscultation; the arteries were hard and tortuous; the pulse small, over 100, arrhythmical; œdema of the ankles; no albumen in the urine. Diagnosis: valvular heart-trouble and arteriosclerosis. Digitalis had been tried, but without success. Dr. Nagubnoff prescribed, one after another, hypodermic injections of strychnia and caffeine-sodium benzoate, in addition to strophanthus. The patient used these remedies for a fortnight. The œdemata disappeared; dyspnœa, feebleness, cough, however, remained in *statu quo*. On account of the strength of these symptoms, Dr. Nagubnoff prescribed *Sperminum-Poehl* hypodermically. After three injections the general condition of the patient materially improved. Cough and pains abated. The patient spent the nights more quietly; the pulse became fuller; but the arrhythmia still continued. Then *Sperminum-Poehl* was injected every third day; the general condition improved permanently; after ten days another injection was given, and after another ten days the last was given, as the patient did not wish to continue the treatment, because in spite of the arrhythmia, she felt so well that she could resume her customary life. During a year she remained perfectly well, and needed no medical assistance. From this time on all trace of the patient was lost.

OBSERVATION OF DR. G. V. HIRSCH, PHYSICIAN-EXTRAORDINARY TO
HIS MAJESTY THE CZAR OF RUSSIA. ARHYTHMIA CORDIS.

In a ninety-one-year-old patient, Count H., whom he had under treatment for thirty years, Dr. v. Hirsch had occasion to observe that *Sperminum-Poehl* has a stimulating and regulating effect on all the physiological processes of the organism. In spite of a comparatively great vigour the patient began to complain of feebleness. Although no pathological sounds were perceptible in the heart, it pulsed quite arhythmically; there were frequent spells of dizziness—doubtless symptoms of sclerosis of the cerebral arteries. Dr. v. Hirsch prescribed *Essentia Spermini-Poehl* to the patient twice a day; this he took regularly for a whole year. Without being asked how the medicine operated he said at every visit of the doctor: "These drops have done me an enormous amount of good; I am quite a different man since I have been using them." The feet became stronger and the self-consciousness much better; the spells of dizziness diminished and the arhythmia of the heart recurred much less frequently.

OBSERVATIONS OF DR. PANTSCHENKO,⁵⁰⁸ PROFESSOR KOSTJURIN,⁵⁰⁹
AND DR. FILIPPS.⁵¹⁰ ARTERIOSCLEROSIS, ANGINA PECTORIS,
AND EMPHYSEMA PULMONUM SENILIS.

In a patient, 72 years old, who was affected with general arteriosclerosis with spells of angina pectoris, continuous dizziness, tinnitus aurium, sleeplessness, and constipation, Dr. Pantschenko⁵¹¹ after thirteen injections of *Sperminum-Poehl* found cessation of the dizziness and tinnitus, improvement as to sleep and in the general condition.

In a case of angina pectoris of eight years standing, Professor Kostjurin,⁵¹² after eleven injections of *Sperminum-Poehl* found disappearance of the attacks and a considerable improvement in the general condition.

As in anæmia, preparations of iron become more effective by the simultaneous use of Spermin, so in Dr. Philipps's⁵¹³ case of emphysema pulmonum with disturbance of compensation, digitalis in half-grain doses took effect after injections of Spermin, while before it had been ineffective, though administered in large doses.

OBSERVATION OF DR. MAXIWOMITSCH,⁵¹⁴ AFFECTION OF THE
HEART AND THE BLOOD-VESSELS.

In compensated valvular heart-trouble, in fatty degeneration of the heart, in weakness of the same in consequence of degeneration of the heart-muscle from infectious diseases, age, alcoholism, etc., Dr. Maximowitsch obtained in less than two months some very good and lasting results by an alternative treatment with *Sperminum-Poehl* and iodides. In arteriosclerosis Dr. Maximowitsch also obtained striking success with *Sperminum-Poehl* (*Essentia Spermini-Poehl*) used alternately with preparations of iodine and arsenic. There was great improvement of the general condition, want of breath when going upstairs or walking was not so noticeable; while there was pronounced relief of other symptoms, as dizziness, polyuria in night-time, stranguria, heaviness in the extremities, numbness of the points of the fingers, with special improvement of vision in cases of presbyopia. Besides there was a considerable decrease in the excretion of uric acid in cases of arteriosclerosis with uric acid diathesis. As in these patients the impairment of their condition takes place mostly in spring and autumn, Dr. Maximowitsch advises his patients to take such a course of treatment regularly during those periods of the year.

OBSERVATION OF DR. ROSCHTSCHININ,⁵¹⁵ NEPHRITIS CHRONICA.

In further reference to diseases of the kidneys, Dr. Roschtschinin observed in one case of nephritis chronica a considerable aggravation taking place after several injections of Spermin, and therefore considered it as contra-indicated in nephritis. He deemed the cause of the harmful action to be an increase in the pressure of the blood. That this conclusion, which was drawn from this one observation, is not tenable has since been demonstrated by Podkopajeff,⁵¹⁶ Sokoloff,⁵¹⁷ and Goldberg,⁵¹⁸ who convinced themselves of the favourable influence of *Sperminum-Poehl* in inflammatory processes in the kidneys.

§ 149. Explanation of the therapeutic action of *Sperminum-Poehl* in weakness of the heart from affections of the heart and lungs

The regulating influence of *Sperminum-Poehl* on the action of the heart as well as the tonus of the blood-vessels apparently depends finally on the influence on the nervous system, which we have already discussed; that is, on the cerebral centres, the heart-ganglions, and the vasomotors.

These organs, as well as the heart-muscle, are delivered of the products of metabolism that are accumulated in them by the increased intraorganic oxidation, and in this way are aided to further activity. In §117 it has been clearly shown that among the intermediary products of metabolism are also such as represent more or less strong heart-poisons (as, for instance, neurin, xanthin, etc). In the same section we also pointed out in what manner such toxic compounds are by oxidation changed to harmless ones.

Very instructive is the observation of Dr. Filippis, which, as he later says, has since been corroborated several times. On the one hand he reports a case in which small doses of digitalis were effective in combination with Spermin, while without it the effect was absent. On the other hand, he has succeeded, by the simultaneous use of Spermin, in avoiding the so-called cumulative action of digitalis in cases of its long-continued employment. This fact can be explained in the following way. The products of fatigue, which, during continued employment of digitalis, naturally accumulate in the heart-muscle, will, should the oxidation, *i.e.*, the removal, be imperfect, finally lead to serious interference with the heart-action. Under the influence of *Sperminum-Poehl* these products of fatigue are oxidised, and the heart-muscle is freed from them.

The highly interesting observations of Prof. Huchard⁵¹⁹ on the arhythmical and tachyrhythmical forms of cardiosclerosis show how large a part the auto-intoxications play in heart

diseases. When, in addition to this, we consider that *Sperminum-Poehl*, by the increase of the textural respiration, causes the formation of splitting-products of albumen of small molecular weight, thereby increasing the osmotic force in the textural juices, this suffices to facilitate the work of the heart. In consequence of the increase of the osmotic pressure the kidney (as lymph-heart) is enabled to produce a stronger suction, and in this way it relieves the heart. Hence, and with reason, Zikel⁵²⁰ considers *Sperminum-Poehl* as an osmotic and a heart-remedy.

At the same time, however, by the increase of the osmotic pressure in the textural juices, as well as the increased energetic function of the kidneys caused thereby, the work of the heart is relieved. Recently we have obtained direct evidence showing that toxins which check the heart in its function are destroyed by *Sperminum-Poehl*. This was accomplished by the really classical experiments of Prof. A. Kuljabko.⁵²¹

Prof. Kuljabko has demonstrated * in isolated hearts of warm-blooded animals (see § 16) that under the influence of chloroform, nicotin and alcohol the heart-action shows some pronounced anomalies, especially arrhythmia.

After the introduction of very small quantities of *Sperminum-Poehl* these anomalies, caused by the poisons named, are suspended, and the heart-action is brought again to the normal. As by the influence of *Sperminum-Poehl*, first, the processes of oxidation are increased; secondly, the decreased osmotic pressure is brought to the normal; and, thirdly, the toxins are rendered non-toxic or even destroyed by the great energy of the processes of oxidation, the therapeutic effects obtained with *Sperminum-Poehl* in weakness of the heart attributable to affections of the heart and lungs find a precise scientific explanation.

Prof. Kuljabko,⁵²² in his work on the pharmacological observations on isolated hearts has demonstrated with heart-curves the influence of the poisons on the heart and the suspension of their action. For an account of these highly

§ 150. Removal of the disturbance of the function of the heart by *Sperminum-Poehl*

* In consequence of a printer's error which was overlooked in the proof-reading of the original Russian edition, as well as in the German translation, a mistake has crept in, when it is said that the experiment lasted five days; it really lasted only two days.

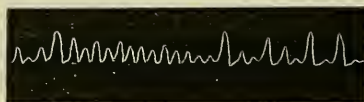
interesting observations we must refer the reader to the original.

The work of Prof. Kuljabko has quite recently been confirmed in the dissertation written by Dr. Kakowsky,⁵²³ under the able supervision of Prof. Kobert, in Rostock. Extracts will be given to show the results of the investigations of Dr. Kakowsky on the action of *Sperminum-Poehl* on the isolated heart, while illustrations of them will be furnished by means of photographic reproduction of his curves.

Dr. Kakowsky used the solution of *Sperminum-Poehl* in the same way that he added *Sperminum-Poehl* (from the ampullæ for injection) to Locke's fluid. The statements as to the concentration refer to the proportion between the chloride of Spermin and Locke's solution.

In order to signify the work of the heart Kakowsky appeals to the sphygmographic curves and for the determination of the energy of the heart-action, he employs the symbol Q, which signifies the quantity (in ccm.) of the fluid which, by the heart-systole, the heart ejects in one minute; while P expresses the pulsation of the heart in one minute.

The very pronounced arrhythmia of an isolated rabbit-heart (Experiment 8), which was irremovable by means of infusion of digitalis (curve 41), entirely disappeared after the introduc-



41. Curve of a rabbit's heart. Pronounced Arrhythmia.

tion of *Sperminum-Poehl* (1 : 6600), which at the same time increased the size (curve 42).

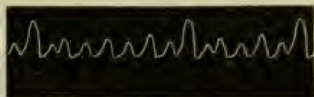


42. Pronounced Arrhythmia abolished by the use of *Sperminum-Poehl*.

Here Kakowsky observed the dilatation of the coronary arteries under the influence of *Sperminum-Poehl*, and from

his manifold experiments arrived at the conclusion that *Sperminum-Poehl* dilates the coronary artery more than any other of the twenty-eight means which he examined (p. 141).

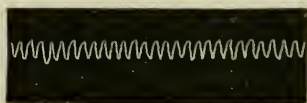
When the employment of Spermin-containing fluid was suspended, the arhythmia reappeared. (Curve 43.)



43. Reappearance of Arhythmia following the stoppage of Sperminum-Poehl.

When the *Sperminum-Poehl* solution (1 : 6600) was again introduced, the arhythmia again disappeared. From this Kakowsky concluded that *Sperminum-Poehl* not only improves the heart-action by dilatation of the coronary arteries, but, thanks to its specific stimulating action, it also beneficially affects the motoric apparatus of the heart.

In Experiment 10, Kakowsky observed the influence of the solution of *Sperminum-Poehl* (1 : 5000) on the weakened heart of an old tom-cat. Before the action of the Spermin (curve 47) it measured but $2\frac{1}{2}$ mm., while after it was found to be $7\frac{1}{2}$ mm.



47. Curve of weak heart in an old cat.

The quantity (Q) of the fluid ejected by the systole of the heart previous to the action of the Spermin was very small :

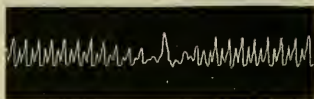


48. Pronounced increase of amplitude through the use of Sperminum-Poehl.

$Q=17$. After the action of *Sperminum-Poehl* its value was nearly doubled : $Q=33$. The pulse-rate (P) went down at first from 122 to 100, to return afterward to the normal 116.

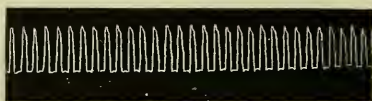
When Kakowsky suspended the action of the Spermin and passed common Locke's fluid (unmixed with Spermin), its size fell to its former value, while the value Q dropped to 13.

In Experiment 11, on the heart of a fat old tom-cat, in which by veronal a high-grade arrhythmia had been produced (curve 50), Dr. Kakowsky used the same *Sperminum-Poehl* solution (1 : 5000).



50. Pronounced Arrhythmia of the heart of a fat old cat after Veronal poisoning.

Immediately after the action of the Spermin the arrhythmia entirely disappeared and the size became nearly three times as great (curve 51).



51. Regulated heart effect and large increase of amplitude following the use of *Sperminum-Poehl*.

The quantity (Q) of the fluid ejected by the systole of the heart was increased from 20 to 40, and the pulse-rate dropped from 160 to 124. Upon the suspension of the Spermin-action considerable arrhythmia again appeared, the size diminished, while the value Q fell to 27 and the pulse-rate rose to 180.

Experiment 5.—A weakened rabbit-heart was treated with a *Sperminum-Poehl* solution (1 : 6000). At once a surprisingly great increase in its size and of the value of Q took place. The measurement within five minutes rose from 2 mm. to 7 mm. and the value Q from 12 to 44. The pulse-rate at the beginning was slower, falling from 108 to 96; but returned later on to 108. During the passing of normal Locke's solution the condition changed for the worse. Q became = 13.5, and the size = 3 mm. It will be observed, however, that the values are higher than in the beginning of the experiment. In this Kakowsky recognises a very important therapeutic factor, namely, that the *Sperminum-*

Poehl has not only a stimulating effect on the heart but also a lasting favourable after-effect, to which he calls special attention (p. 137).

Experiment 6.—A rabbit-heart poisoned with digitoxin pulsed very slowly ($P = 76$), very feebly ($Q = 5.5$ ccm.), and arrhythmically. Under the influence of *Sperminum-Poehl* (solution 1:6000) the arrhythmia disappeared, the size increased, as did the value Q (to 10 cc.), and the pulse-rate to 144—in short, the heart-action returned to the normal. After the stoppage of the Spermin-action the favourable symptoms disappeared; but the arrhythmia did not return.

Therefore, says Kakowsky (p. 137), *Sperminum-Poehl* will remove the arrhythmia and other anomalies of the heart-action (bradycardia), which appear in intoxications of the isolated heart with heart-poison (*i.e.*, digitoxin).

These experiments of Kakowsky agree entirely with the observations made by Filippis and others at the bedside. They established the fact that the much-dreaded cumulative action of digitalis can with *Sperminum-Poehl* not only be removed but also prevented. On the other hand, the experiments of Professor A. Kuljako and of Kakowsky furnish an explanation of the observations made first by the sick bed by Dr. v. Hirsch⁵²⁴, on the favourable influence of *Essentia Spermini-Poehl** on the arrhythmia of the heart both of functional and organic origin.

All that we have said makes it clear that in cases in which much depends on a quick increase of the osmotic pressure and on the influence on some toxins eventually present, in the absence of œdemata, clysmata of *Sperminum-Poehl sicc. pro clysm.* are chiefly to be recommended. We have before said that in this way the vital energy of the organism is increased and its fight against the pathological processes in the lungs facilitated.

The beneficial influence of *Sperminum-Poehl* so frequently observed in kidney- and heart-disease as, for instance, the disappearance of the œdemata, is in part to be accounted for by

* The less favourable results which Kakowsky obtained with *Essentia Spermini-Poehl* in experiments made on the isolated heart, are, as he himself admits (p. 147), chargeable to the accretions occasionally found in the essentia which apparently in the isolated heart disguise the effect, while in patients the *Essentia Spermini-Poehl* promptly produces the favourable effect, as is specially noted by Dr. v. Hirsch.

the influence on the heart-action to which we have just referred. The disappearance of the symptoms of irritation in the kidneys (the hyaline and finely granulated cylinders and the albuminuria) is to be explained by the oxidation of the intermediary products of metabolism. Some of them—as, for instance, xanthin and hypoxanthin—are capable of irritating the kidneys and even of producing nephritis. Under the influence of Spermin therapy, however, they are oxidised to harmless compounds.

In cases of auto-intoxication irritation of the kidneys has repeatedly been observed, and Professor Senator,⁵²⁵ Robin,⁵²⁶ Bouchard,⁵²⁷ and Dr. Praetorius,⁵²⁸ have all drawn attention to the connection between auto-intoxication and albuminuria.

There are no clinical observations on record as to the employment of the *Sperminum-Poehl sicc. pro clysm.* in œdemata. On the ground of physiological-chemical argument, however, Professor Poehl has pronounced against the use of Spermin-clysms with physiological salt in œdema. He did so for the reason chiefly that apparently in œdema, in consequence of the insufficient action of the kidneys, some osmotically active constituents accumulate in the textural juices, and the œdema appears to be a self-protective measure of the organism for the relief of the textural juices from an excessive osmotic pressure. The introduction of physiological salt with clysms intended to be retained would, therefore, be irrational in œdema. The employment of *Sperminum-Poehl pro injectione*, however, or the *Essentia Spermini-Poehl per os* is not only theoretically but also practically justified. This is proved on the one hand by clinical observations, and on the other, the experiments made in the laboratories show that by the use of Spermin the work of the kidneys is relieved. In this way the irritation of the kidneys is diminished or suspended, while, further, *Sperminum-Poehl* has a permanent stimulating influence on the heart.

VI. Intoxications.

A. Organic Poisons.

There is no very great number of published observations on the employment of *Sperminum-Poechl* in chloroform-narcosis. Nevertheless in practice it is in such cases extensively used. Of special interest are the observations of Prof. Weljaminoff. He was the first physician who used it in chloroform-narcosis. These early observations which are of great practical importance, deserve a thorough discussion.

§ 151. Clinical observations on the therapeutic action of *Sperminum-Poechl* in chloroform-narcosis

OBSERVATIONS OF PROFESSOR WELJAMINOFF,⁵²⁹ PHYSICIAN EXTRA-ORDINARY TO HIS MAJESTY THE CZAR. SPERMINUM-POEHL IN CHLOROFORM NARCOSIS.

CASE 1.—Patient, female, 39 years old, was extremely anæmic. She was very weak from loss of blood, and suffered constant pain. Heart-action weak. Her appearance was not all at encouraging, so that Professor Weljaminoff was in doubt whether she would be able to withstand so severe an operation (fibromyoma corporis et cancer colli uteri) as the occasion demanded. He therefore hesitated a long time whether he should undertake the operation or not. In accordance with the special wishes of the patient to submit to the operation, he concluded to operate and to use at first *Sperminum-Poechl*.

Here it should be remarked that in this, as well as in the case following, the patient did not know what was injected. In any case, beyond the surgeon in charge and two of his assistants, none of the hospital staff knew anything about it.

On November 18, 19, and 21 *Sperminum-Poechl* was hypodermically injected (1 ampulla each day). The general condition improved somewhat; the heart-action was undoubtedly stronger and the pulse fuller. On November 23 a further injection was made, and the operation performed. One after another, the supravaginal amputation of the womb and the resection of the column and of the remaining part of the corpus uteri were made per vaginam. The operation lasted two and a half hours. The narcosis was excellent, and during the whole time not the least weakness of the pulse or trace of shock was noticeable, although an enormous quantity (six ounces) of chloroform had been consumed. Patient did not wake until about two hours and a half after the close of the operation, and then no symptoms of feebleness appeared. The pulse had remained the same as before the operation. Although immediately before the operation considerable symptoms of irritation appeared (possibly sepsis), as vomiting, severe meteorism, acceleration of the pulse up to 130 per minute, with subnormal temperature—there was no weakening of the heart-action, and the patient stood the operation splendidly; the reconvalescence beginning as early as the fifth day. Patient was very soon discharged perfectly cured.

CASE 2.—Woman of 45 years was so weak and so poorly nourished that for a long time Professor Weljaminoff could not resolve upon perform-

ing the operation (cancer recti). On January 18, 20, and 22 (the date of the operation), three injections of Spermin were given. After resection of the os coccygeum a piece of the rectum, ten cm. long, was removed, while two cm. from the anal opening on were saved. The peritoneum was laid bare to a considerable extent. During the ligation of the rectum there was great loss of blood. The operation lasted an hour and a half; 90 grammes (three ounces) of chloroform were used. During the operation as well as upon its termination, there was no sign of shock or collapse; excellent narcosis. This was Professor Weljaminoff's eighth case of extirpation of the rectum. Patient was much weaker and more emaciated than any of his former cases, but had nevertheless withstood the operation—which may very properly be considered one of the severest—more easily than any other of the patients.

CASE 3.—All that has been said of the preceding cases might be repeated of this with the addition that the patient had a tubercular affection of the left lung. She was 26 years old. Great papillomata of both ovaries and ascites. Patient was extremely emaciated, weak and anæmic. Forty pounds of fluid were removed from the abdominal cavity with the trocar. On February 20 after hypodermic injection of one ampulla of *Sperminum-Poehl* ovariectomy bilateralis was performed. The operation lasted an hour; fifty grammes of chloroform were used. The narcosis as well as the condition immediately after the operation were ideal.

CASE 4.—Upon a woman of 62 years an operation was to be performed for a goitre of the size of the fist, located on the left side. There was well-marked arteriosclerosis with arrhythmic pulse. On February 16, 18, 20, 23, and 25 (the date of the operation) injections of *Sperminum-Poehl* were given. After the first injections the pulse became fuller and more regular. Partial strumectomy. The operation lasted an hour and a quarter. Patient stood the operation splendidly.

Generally Prof. Weljaminoff satisfied himself that all the patients who were considered unfit to undergo operations after the use of *Sperminum-Poehl*, stood the narcosis as well as severe traumata with remarkable ease.

The cases above reported present features of special interest when it is considered that, as already mentioned, the patients did not know the nature of the injection used. The idea that there was auto-suggestion is therefore altogether excluded.

Since that time, in severe operations Prof. Weljaminoff always uses hypodermic injections of *Sperminum-Poehl*.

For a communication addressed to the Paris Academy of Medicine, Dr. Chorwath⁵³⁰ has edited the material provided by Prof. Weljaminoff.⁵³¹ There were sixty-one severe operations, twenty-eight without, and thirty-three with preceding injections of *Sperminum-Poehl*. From these observations Dr. Chorwath draws the following conclusions: (1) Exhausted, marasmic and elderly individuals, as well as alcoholics and hysterics, when under the influence of *Sperminum-Poehl*

stand much larger quantities of chloroform and a much longer narcosis than without it. (2) The narcosis appears to take a smoother course : complications, as vomiting, asphyxia, imminent weakness of the heart, etc., are of rare occurrence. After severe operations, the shock, which is so much dreaded, has never been observed.

The employment of *Sperminum-Poehl* in surgical practice (before the chloroform-narcosis and as a stimulant in severe operations) is due in the first place to experiments made on animals by Prof. Prince Tarchanoff. He has demonstrated that the experiment-animals stood the chloroform better on the simultaneous use of Spermin, and that the healing of the wound took place more easily and quickly in sperminised animals. It has been shown by Poehl,⁵³² by the experiments mentioned in § 72 and the following, and by Kuljabko⁵³³ (§§ 16 and 50), that under the influence of chloroform the blood loses its power of transferring oxygen, and that the addition of *Sperminum-Poehl* restores this power.

When comparing the urine before and after chloroform-narcosis Poehl⁵³⁴ has in the latter case always found an increased quantity of the nitrogenous intermediary products of metabolism, that is, Robin-Poehl's coefficient of oxidation was considerably decreased. Direct tests for the xanthin- and kreatin-groups have always shown a considerable increase of these compounds in the urine.

Profs. Bouchard and Laborde have experimentally demonstrated already that in animals chloroform produces irritation of the kidneys with albuminuria. All these observations agree with those of Eisendrath and Naebod.⁵³⁵ The latter has shown that after chloroform-narcosis in a series of cases pronounced symptoms of irritation appeared in the kidneys. He made systematic examinations of the urine after chloroform-narcosis in fifty-seven children from one to fifteen years old. Results : In four cases he found serum-albumen, in six cases nucleo-albumen, in one case both. In thirteen cases after the narcosis casts were found in large quantities. Sugar could not be demonstrated in these cases ; often, however, an increased excretion of creatin was found. In ten cases aceton was found, in six acetacetic acid, in fourteen cases, both the compounds simultaneously. In the chloroform-narcosis the urochloral acid discovered by

v. Mering, and the trichlormethylglycuronic acid found by Kast appear in the urine; the symptoms of irritation of the kidneys, however, can be explained without special consideration of these compounds by an increased amount of xanthin-bodies in the urine. This opinion finds strong support in the experiments of Gaucher already mentioned. He observed in guinea-pigs, after injection of xanthin, "Nephrite épithéliale," after introduction of hypoxanthin, albuminuria. As we know that the xanthin- as well as the kreatin-compounds under the influence of intraorganic oxidation are changed to higher grades of oxidation, by which they lose their toxicity and gain in diffusibility, the favourable results obtained with Spermin find their explanation. It operates as a preventive against the appearance of the xanthin-intoxication and the irritation of the kidneys, that is, the nephritis caused by it.

The relief of the function of the kidneys under the therapeutic influence of *Sperminum-Poehl* has already been discussed in § 149. In the chloroform-narcosis we have still to take into consideration that under the beneficial influence of *Sperminum-Poehl*, the weakness of the heart which eventually occurs is removed (§ 97). We believe that this factor is just as important as the removal of the irritation of the kidneys. Thirdly, the increase of the osmotic pressure, which is decreased by the narcosis, is in favour of the employment of *Sperminum-Poehl* in chloroform- and ether-narcosis.

A. Desgrez and M. Nicloux⁵³⁶ drew attention to the development of carbon oxide in the blood during intoxication with chloroform. Chloroform is "in vitro" at the average temperature in aqueous alkaline solution decomposed under formation of carbon oxide. Under the assumption that in the organism the chloroform is exposed to similar conditions. Desgrez and Nicloux tested the blood of the experiment-animals both before and after the chloroform-narcosis for carbon oxide. The increased power of reduction of the blood which is present here is explained by these authors as owing to the carbon oxide it contains. According to the calculations of these investigators, based upon the results of the animal-experiments, during a narcosis lasting two hours, a man would produce 26 ccm. of carbon oxide; a quantity which, according to Gréhan, has toxic effects.

Poehl's experiments with carbon oxide on blood show

that the power of the blood to transfer oxygen is lowered by the influence of carbon oxide and restored by the addition of *Sperminum-Poehl*. This experiment "in vitro" is corroborated by the following observation of Dr. Podkopajeff. He obtained highly satisfactory results with *Sperminum-Poehl* in two cases of severe poisoning with carbon oxide.

Further, in consideration of the formation of carbon oxide in the chloroform-narcosis the increase of the intra-organic oxidation by the use of Spermin is directly indicated. The same idea has apparently occurred to Professor L. Prochownik,⁵³⁸ who in his gynæcological clinics always has oxygen inhaled after the chloroform-narcosis.

Poehl says a further indication for the employment of the *Sperminum-Poehl* in chloroform-narcosis lies in the fact that the alkalinity of the blood is lowered in chloroform-narcosis. This appears on the one hand from numerous urinalyses made by Poehl, and on the other hand by direct determinations of the alkalinity of the blood (Jacob, Peiper).

The decrease in the alkalinity of the blood from the chloroform-narcosis causes a direct lowering of the textural respiration. As we have seen, on the other hand, the chloroform directly lowers the power of the blood of transferring oxygen. We have therefore two factors which simultaneously check the intra-organic oxidation. If any other forces are added operating in the same direction, the conditions are given under which the complication of symptoms which is named "shock" may occur. As predisposing causes Villaret, as well as others, mentions psychic influences (anxiety, excitement, etc.); hence, factors which accompany irritation, such as acidulation of the nervous tissue (v. Leyden and Eulenburg call the shock which appears under such circumstances "psychic trauma"). Villaret further names conditions of inanition, affections of the heart, the brain, and the liver as predisposing factors for shock. As one of the direct causes Professor v. Bergmann cites operative interferences in the abdominal cavity which, besides others, produce nervous irritation on a comparatively large surface. All the above-mentioned factors act in the same manner as the chloroform-narcosis—they lower the intra-organic oxidation. From this point of view the non-appearance of shock after the use of Spermin preliminary to grave operations, to which

Professor Weljaminoff points, can theoretically be explained in a satisfactory manner.

§ 153. Clinical observations on the therapeutic action of *Sperminum-Poehl* in ether-narcosis

To the above-mentioned observations of the action of *Spermin* in chloroform-narcosis the following case of ether-narcosis of Dr. Krieger (Chicago) should be added.

OBSERVATION OF DR. KRIEGER. ETHER-NARCOSIS.

In order to satisfy himself whether *Spermin* really has an influence on the course of the narcosis, Dr. Krieger made observations on a patient in a Chicago infirmary who had to be narcotised several times. It was a thirty-nine-year-old man who suffered with piles, for the removal of which Dr. Krieger had to perform Lange and Whithead's operation. Before the narcosis the patient received a hypodermic injection of *Sperminum-Poehl*. The narcosis lasted an hour and a half; its course was excellent, and the patient felt perfectly well when he woke up. Eight days later he was again narcotised for the purpose of removing the stitches, without the use of *Spermin*. The narcosis lasted only fifteen minutes; after the awakening, however, the patient complained of nausea and a generally distasteful feeling.

OBSERVATIONS OF DR. PODKOPAJEFF.⁵⁴⁰ POISONING WITH CARBON OXIDE.

§ 154. Clinical observations on the therapeutic action of *Sperminum-Poehl* in carbon oxide poisoning

Dr. Podkopajeff reports that injections of *Sperminum-Poehl* have remarkable effects in carbon oxide poisoning. He established the favourable action in two cases of grave poisoning (in one case three and a half syringefuls of *Sperminum-Poehl* were injected in the course of two hours and a half).

Sperminum-Poehl is also of the greatest value in chronic alcohol-intoxication.

OBSERVATION OF PROFESSOR STANGE.⁵⁴¹ ALCOHOLISMUS.

§ 155. Clinical observations on the therapeutic action of *Sperminum-Poehl* in alcoholism

Professor Stange was the first to use *Sperminum-Poehl* in the form of hypodermic injections in one case of delirium tremens. He succeeded in shortening the disease materially and in avoiding the use of a number of narcotics which the patient had needed in former attacks, for which he had been treated by the same physician.

OBSERVATION OF DR. J. SOKOLOFF.⁵⁴² ALCOHOLISMUS.

Merchant O., 34 years old, had been for nine years a periodical drunkard and had several times every year severe spells of alcoholism. After such an attack patient became so sick that he could not leave his bed. The usual doses of chloral, paraldehyde, and strychnine did not quiet him. They even aggravated his condition to such an extent that he could not raise his hand. Sleep and appetite were entirely gone. Three injections of *Sperminum-Poehl* were made within two days. The patient left his bed; appetite and sleep returned. He felt so far well that he could resume his usual occupation.

The beneficial action of *Sperminum-Poehl* in drunkards has also been demonstrated by Dr. M. Goldberg,⁵⁴³ Dr. S. Shichareff,⁵⁴⁴ etc.

Very favourable results were obtained in alcoholism by Dr. Pantschenko and Dr. Lion from a combined treat-

ment with *Sperminum*- and *Cerebrinum-Poehl* which we shall discuss more thoroughly when dealing with cerebrin.

In connection with these observations on the action of *Sperminum-Poehl* in chronic alcoholism we wish to point to the fact that the intra-organic oxidation is in such cases decreased.

This is shown by the observations of Professor N. Simanowsky and Schumoff,⁵⁴⁵ who made their experiments on men and animals after the method of Professors Nencki and Sieber.⁵⁴⁶ The authors mentioned explain this phenomenon as owing partly to the direct inhibition of the processes in the protoplasm and partly by the fact that alcohol, for its own oxidation, requires some atomistic oxygen. On the other hand, Z. Donogany and Tibald,⁵⁴⁷ found that the quantity of uric acid increases not only absolutely, but also in proportion to the excretion of nitrogen, which necessarily affects Robin-Poehl's coefficient of oxidation.

From these physiological-chemical points of view the employment of *Sperminum-Poehl* in chronic alcoholism is theoretically justified. The influence of the Spermin therapy on diseases of the nervous system and the heart which so often follow alcoholism, has already been discussed.

Professor Polotebnoff and Dr. Woskresenski report a case in which by the use of mercury an enormous salivation was caused, which ceased immediately after the employment of *Sperminum-Poehl*, so that the mercurial therapy could be continued.

Apparently, as we shall see later, the most important duty of the Spermin-therapy in syphilis is to restore the decreased tonus of the organs to the normal.

B. Toxins.

Sperminum-Poehl in Syphilis, Erysipelas and Cholera Asiatica.

In the above-mentioned diseases observations on the employment of *Sperminum-Poehl* have been made by Schichareff, Huebbenet, Injasewski, Professor Schwimmer, Wichert, Nikolski, v. Rossi, Minajewski, and Besser, as well as others.

OBSERVATIONS OF DR. SHICHAREFF.⁵⁴⁸ SYPHILIS.

Dr. Shichareff has made a series of observations, at first alone and subse-

§ 156. Explanation of the therapeutic action of *Sperminum-Poehl* in alcoholism.

§ 157. Clinical observation on the therapeutic action of *Sperminum-Poehl* in mercurial therapy

§ 158. Clinical observations on the therapeutic action of *Sperminum-Poehl* in syphilis and erysipelas

quently in collaboration with Dr. Huebbenet, and he has convinced himself of the beneficial influence of *Sperminum-Poehl* in all cases of lues gummosa. The considerable improvement in the general condition is in his opinion to be placed to the credit of the increase in the blood-pressure and of the muscular strength.

OBSERVATIONS OF PROFESSOR SCHWIMMER.⁵⁴⁹ SYPHILIS.

Professor Schwimmer obtained in six cases very good results from the employment of *Sperminum-Poehl* in syphilis (rupia syphilitica). In all the cases he had to deal with grave affections in which treatment with mercury had proved detrimental, while *Sperminum-Poehl* produced an increase of the metabolism of the nitrogen, prevented the further spread of the ulcerations, and even favoured their closing within a short time.

OBSERVATION OF DR. WICHERT.⁵⁵⁰ ERYSIPELAS.

In a case of erysipelas of the face with well-pronounced condition of depression, Dr. Wichert tried *Sperminum-Poehl* in order to improve the general condition of the patient. Neither on the local processes nor on the temperature did Spermin have any influence; the apathy of the patient, however disappeared for some time after each injection. The patient became more lively, felt better and asked for something to eat on each occasion.

§ 159. Explanation of the therapeutic action of *Sperminum-Poehl* in syphilis

About sixteen years ago Poehl⁵⁵¹ called attention to the fact that the urine of the syphilitic always has a low co-efficient of oxidation. Consequently in every case of syphilis we have, besides other things, to deal with an accumulation of intermediary products of metabolism. However the symptoms of auto-intoxication appearing here may differ, according to the tissues in which they take place, they all have the chemical characteristics of the decreased textural respiration. If we finally consider that treatment with mercury, which is so unavoidable in the syphilitic, again produces a decrease of of the intraorganic oxidation* as one of the gravest by-effects, we must admit that the suggestion of Professor Schwimmer, to give Spermin both before and after the treatment with mercury, is certainly rational. In the interest of Science his untimely death is to be deplored. What has been said about the treatment with mercury applies also to that with iodides which often becomes so necessary in the later stages of syphilis. Further, the author above mentioned, as well as Schichareff, Huebbenet, etc., by mere treatment with Spermin without mercury has also obtained some favourable results.

* Poehl's blood-experiments show that the power of the blood to transfer oxygen is "in vitro" very much decreased by the addition of a solution of corrosive sublimate. This accounts for the injurious influence of mercury on the intraorganic oxidation.

The large number of the urinalyses made by Professor Poehl of people affected with syphilis shows that in this disease the intermediary products accumulate in the organism and cause a lowering of the textural respiration which, as is known, is yet doubled by treatment with mercury. The successes obtained in syphilis are satisfactorily explained by the action of Spermin as a ferment of the intra-organic oxidation and as a nervous stimulant, without any intention on our part of claiming that it is a specific remedy.

The clinical observations on the action of *Sperminum-Poehl* in cholera asiatica have been made in great numbers (among others) by v. Rossi,⁵⁵² Nikolsky,⁵⁵³ Besser,⁵⁵⁴ and Milajewsky,⁵⁵⁵ and the histories of the cases have been reported very thoroughly with their respective urinalyses. We confine ourselves here to giving several short extracts from the records of the Alexander-Semenoff's Guard Hospital and refer the reader to the detailed reports in the book by Professor Dr. A. v. Poehl: "Die physiologisch-chemischen Grundlagen der Spermintheorie nebst klinischem Material zur therapeutischen Verwendung des Sperminum-Poehl" (pp. 282-305).

OBSERVATIONS FROM THE ALEXANDER-SEMOFF'S GUARD HOSPITAL, BY
DRS. E. V. ROSSI,⁵⁵² BESSER,⁵⁵⁴ MILAJEWSKY.⁵⁵⁵
CHOLERA ASIATICA.

CASE 1.—Mild form of cholera; treated exclusively with *Sperminum-Poehl*. Recovery. On July 22 the quantity of the urine was 150 ccm., on the 23rd 600 ccm.; on both days the urine contained albumen; on the 23rd it contained some casts. Later on the quantity of the urine increased to 1600 ccm. The coefficient of oxidation rose from 83.29 (July 22) to 93.18 (August 9). Zerner's coefficient sank from 0.80 to 0.38. The reaction for nitrates always gave a positive result. The quantity of the paired sulphuric acids was at first very large (at the same time the amount of indican in the urine was also increased); later on it decreased and finally reached the normal (August 2 and 9).

CASE 2.—Patient, 23 years old. Diarrhoea, vomiting, and convulsions. Depressed appearance, the pulse, however, was good, the abdomen soft, 5 ccm. of urine. Temperature in the evening 36.18. Convulsions, yellowish watery evacuations. The bacteriological examinations showed the presence of cholera bacilli. Treatment: warm tub-baths, valeriana, coffee, wine, and from July 11 to 17 injections of *Sperminum-Poehl*.

On July 10 albumen and granular casts were found in the urine. The quantity of the urine slowly increased to 1900 ccm. The coefficient of oxidation was on July 10 below the normal; on the 16th, however, it rose to 92.37. Zerner's coefficient sank from 0.99 (in the beginning) to 0.46 (on July 16). The quantity of the paired sulphuric acids was on July 10 very large; at the same time the amount of indican was also increased. As early as July 12, however, it commenced to diminish, reached the normal and then remained constantly the same.

§ 160. Clinical observations on the therapeutic action of *Sperminum-Poehl* in cholera asiatica

After the Spermin treatment the fæces became normal ; the tongue clean ; the pulse good ; and patient was discharged cured on August 3.

CASE 3.—Patient, 24 years old, of weakly build, was taken to the hospital on July 10. Cyanotic condition ; facies Hippocratica. The bacteriological examination made by Dr. Besser showed the presence of cholera bacilli. From July 9 on perfect anuria. Treatment : immediately after he entered the hospital, hot tub-baths, castor oil, tannic acid, opium, valeriana, ether, coffee with cognac. As the condition of the patient did not improve, in the evening of July 10 an injection of *Sperminum-Poehl* was administered to him. The further treatment consisted exclusively of injections of Spermin and infusions of normal salt solution to which some *Sperminum-Poehl* was added (1 ampulla *Sperminum-Poehl* to 1 litre of solution).

July 11 eleven passages. Temperature in the morning 36, and in the evening 37.4. The vomiting became rarer and disappeared entirely towards evening, after the infusion. The anuria continued—four injections of Spermin and one infusion of normal salt solution to which some *Sperminum-Poehl* was added.

The urine which was taken with the catheter after anuria lasting three days contained a moderate quantity of albumen and some granular, as well as hyaline, casts. Albumen and casts were still found on the four following days. The quantity of the urine increased from 40 ccm. (on July 12) to 5000 ccm. (on July 18) ; then it slowly sank to the normal quantity. The coefficient of the energy of the oxidation which at first was subnormal (82.15) rose slowly, but steadily, and finally reached (on July 30) the height of 92.43. Zerner's coefficient, in the beginning very high, rose during the first three days still higher, and then, with the recovery of the patient, sank to the normal. The quantity of the paired sulphuric acids was in the beginning very large (with coincident increased amount of indican), and remained equal until July 17 ; then the quantity of the acids named, as well as that of the indican, was normal. As to the reaction for nitrates, it was only once (on July 21) positive.

On August 6 after the repetition of the injections of *Sperminum-Poehl* the stool was normal. Urine, 2300 ccm. Temperature in the morning, 36.4 ; in the evening, 36.7. On August 8 patient was discharged cured.

CASE 4.—Patient, 22 years old, of average build, was taken (on August 12) with diarrhœa (twenty times in twenty-four hours) to which pains in the stomach, convulsions, dizziness, nausea, and vomiting were added. The pulse was soft ; the eyes were a little hazy and sunken in. The abdomen was soft, although in the epigastrium a little painful. Motions colourless. The bacteriological examination of Dr. Besser showed the presence of cholera bacilli. Treatment : hot tub-baths, warming-bottles, warm injections into the bowels, castor oil, essence of mint, ethereal tincture of valeriana, bitter almond water, coffee with cognac, wine, six injections of *Sperminum-Poehl*, one every two hours.

On the termination of the treatment (on August 29) the condition was perfectly satisfactory. The fæces were normal ; urine 12 ccm. The tongue was clean. On September 1 the patient reported for discharge and was discharged cured on the next day.

CASE 5.—Patient, 25 years old, of average build, drank unboiled water on August 27. On the following day pains in the stomach, and diarrhœa appeared ; on the 29th, besides this, vomiting and dizziness. The pulse was weak ; the eyes were sunken in. The respiration was rough ; the frequency 28. The secretion of urine insignificant. Temperature in the evening, 37.8 ; Treatment : warm tub-baths, warming-bottles, tincture of valeriana, ether,

and bitter almond water; injections of *Sperminum-Poehl*. Intravenous infusions of 1000 ccm. of a 0.7 per cent. solution of chloride of sodium.

After the injections of *Sperminum-Poehl* the condition of the patient visibly improved; the faces became normal; the quantity of the urine increased. On September 18 the patient left the hospital in good health.

CASE 6.—Patient, 22 years old, of medium build. The tongue was coated; the eyes were sunken in; the abdomen was soft, but painful. Great apathy. The pulse was fairly full, but easily compressible; the tongue was dry and coated. Colourless stools; vomiting; urine 460 ccm. Temperature in the morning 36.7; in the evening 37.0. Treatment: hot tub-baths, warming-bottles; tincture of valeriana; bitter almond water; coffee with cognac; wine; milk diet. At 3 P.M. injections of *Sperminum-Poehl*; at the same time into the vein of the right hand 480 ccm. of normal salt solution were introduced. Patient visibly recovered under this treatment and left the hospital cured on October 3.

It appears from the clinical material obtainable that *Sperminum-Poehl* has great significance as a therapeutic means for the purpose of preventing the grave cholera intoxication in already existing auto-intoxication or of checking its further development. Therefore, in our opinion, the treatment with *Sperminum-Poehl* is in order especially in the first stages of cholera. In clearly pronounced grave cases, however, the favourable action of *Sperminum-Poehl* is only conceivable as long as the function of the kidneys is not interrupted.

If the favourable results of the use of *Sperminum-Poehl* in cholera asiatica are examined in the light of the views expressed by us in the chapter on immunity and immunisation, the histories of the cases but form an instance justifying this view. In cholera, as in other infectious diseases, the result of the battle of the organism with the intruded elements of infection chiefly depends on the reaction of the menstruum in which the formation of the Spermin takes place. If the juices go beyond a certain degree of acidity, as, for instance, in some cases reported by Poehl in which Zerner's coefficient reached the extraordinary amount of .10, the patient must fall victim to the disease. If the amount of acidity, however, is not so great, the organism may come safely out of the struggle with the infecting elements. In this way the known experiments of Pettenkofer and others, touching the insusceptibility of many people who remain well during an epidemic of cholera and other diseases, are to be explained. As in cholera, so in other infectious diseases, it is not safe to assume that for each kind of infection the formation of a special anti-

§ 161. Explanation of the therapeutic action of *Sperminum-Poehl* in cholera asiatica

toxin takes place. It is much plainer and much more natural to suppose that in the normal organism there exist a number of physiological elements (to which also Spermin belongs), which under favourable circumstances sustain its immunity from the effects of the infection. From this point of view therapeutists try to create favourable conditions of this kind. This can be accomplished by the introduction of *Sperminum-Poehl*, which increases the energy of the oxidation and consequently raises the lowered alkalinity of the blood and the juices and brings them near to the normal.

From the urosemiotic point of view, cholera asiatica presents a very constant complication of symptoms. Unfortunately we find no published statements as to the action of the coefficients of the urine in cholera, beyond the investigations of Poehl, and an article by G. Hoppe-Seyler⁵⁵⁶ who points to the increase of the relative quantity of the paired sulphuric acids (coefficient of Baumann-Morax). Poehl's very numerous urinalyses—of which only a part has been included in the tables given in his book, "Die physiologisch-chemischen Grundlagen der Spermintherapie nebst klinischem Material zur therapeutischen Verwendung des Sperminum-Poehl"—show clearly that in all cases of cholera Robin-Poehl's coefficient of oxidation is considerably decreased, and Zerner's coefficient is materially increased (in some cases even tenfold). According to Quincke and Cantani⁵⁵⁷ the alkalinity of the blood is materially lowered; in the algid stage it is even said to have an acid reaction (C. Schmid,⁵⁵⁸ Roux, Thuillier et Nocard⁵⁵⁹).

The favourable results of the Spermin therapy in cholera may theoretically be explained on the basis of the urosemiotic statements, if we consider the function of *Sperminum-Poehl* as a ferment of the intraorganic oxidation, or as katalysator of the textural respiration. That the textural respiration is sensibly lowered in cholera can easily be seen by a glance at the cyanotic, cold body of the patient.

Poehl has already on several occasions pointed to the fact that *Sperminum-Poehl* cannot be shown to have any influence on the auto-intoxication, especially from the bowels. Therefore *Sperminum-Poehl* cannot be considered as a specific remedy against cholera, but as a stimulant. In cholera, however, we have not only to deal with its stimulating action on the

diseased organism, but also with a change of the biological qualities of the cause of the disease, as Poehl has shown and we have explained in § 16. As already mentioned, in pure cultures of the cholera-bacillus to which *Sperminum-Poehl* has been added, the cholera-red reaction does not take place. This loss of the reducing qualities of the cholera bacillus * causes the diminution of the toxicity of the products of its vital activity. The opinion expressed by Poehl more than sixteen years ago that the cholera bacillus, if developing in a menstruum favouring the processes of oxidation, changes its biological-chemical qualities so far that in this respect it approaches the bacillus of cholera nostras (loss of power of reduction, liquefaction of the nutrient gelatine, etc.), is in accordance with a number of more recent observations. So Hüppe and Fajans⁵⁶⁰ found, that by anaërobic development the cholera bacilli increase in virulence.

Poehl has already on several occasions expressed the view that the immunity of the organism against certain causes of disease directly depends on the condition of the textural respiration at the time. If we now consider the fact that the virulence of some microbes depends on the question whether they develop aërobically or anaërobically the favourable influence of *Sperminum-Poehl*, on different infectious diseases, as cholera, typhoid fever, erysipelas, tuberculosis, septicæmia, is theoretically well founded.

Klebs allows that the immunity against tuberculosis depends on two factors, namely, the degree of the virulence of the tubercle bacilli and the power of resistance of the organism, "the mutual source of which is probably to be looked for in the processes of oxidation inside the organism" (Edwin Klebs⁵⁶¹). The animal-experiments of Professor Prince Tarchanoff, Senator, Loewy, Richter, Dr. A. v. Poehl (§§ 104-110, 116 and 117), furnish the proof that *Sperminum-Poehl* destroys toxins in the organism.

It should be remembered that Armand Gautier⁵⁶² in his classical work, "Les toxines microbiennes et animales" (pp. 356 and 363), reduces the elimination of the toxins to two factors, the oxidation and the excretion with the urine.

* The reducing qualities of the cholera bacilli have been demonstrated in a very convincing manner by Fritz Cahen ("Chem. Centralb.," 1887, p. 1169) in gelatine cultures to which litmus was added.

Consequently, in infectious diseases there are three spheres of action for *Sperminum-Poehl*: (1) the influence on the physiological processes in the diseased organism; (2) the influence on the biological-chemical qualities of the cause of the disease; (3) the influence on the toxins already existing in the organism.

That *Sperminum-Poehl*, as a ferment of the intraorganic oxidation, promotes the oxidation and the elimination of the already existing toxins; that it furthermore is capable of lowering the virulence of the pathogenic microbes, we have already thoroughly discussed in the proper place. The influence of Spermin on the diseased organism itself finds its expression in the promotion of the textural respiration, the increase in the alkalinity of the blood, and the appearance of the immunising leucocytosis.

§ 162. Opinions
of several
clinicians
on Sper-
minum-Poehl

In conclusion let us now quote the opinions of several clinicians, which will be found, *inter alia*, in an article by the Czar's physician, Dr. G. v. Hirsch, on *Sperminum-Poehl*.

Prof. Senator⁵⁶³ has often found in tabes an improvement of the self-consciousness. He accounts for the influence of *Sperminum-Poehl* in several cases of leuchæmia as owing to the enlargement of the number of the polynuclear leucocytes together with an increased destruction of the mononuclear leucocytes.

Prof. Benedict⁵⁶⁴ obtained in two cases of grave affections of the stomach some splendid results with *Sperminum-Poehl*. In the first case (author, 50 years old), the patient had been suffering for eight months with grave dyspepsia, accompanied by excruciating pains in the stomach, loss of appetite, and exhaustion. Even after the first injection an improvement could be seen; after ten further injections, however, the patient enjoyed the very best of health.

In the second case the patient, a lady, suffered with chorea phonetica having a hysterical basis, with coincident vomiting and loss of appetite, going as far even as an antipathy against any kind of food. After the use of Spermin the patient quickly began to recover, and after ten injections she was perfectly well.

Dr. Hofmeister⁵⁶⁵ obtained some good results from the use of Spermin in neurasthenia, tabes, and neurosis from exhaustion. Patient, female, 43 years old, had been suffering for twenty years with fibromyoma of the uterus and

extreme exhaustion from the constant hæmorrhages. Nothing could relieve her suffering. When the patient was no longer able to walk or to busy herself in any manner, Dr. Hofmeister commenced treating her with injections of *Sperminum-Poehl*. She was soon like one newly born; she was once more able to take exercise or visit the theatre, etc. When she felt weak after lasting and tiring work, she quickly went to her physician who again restored her strength in the above-mentioned way.

Prof. A. Eulenburg⁵⁶⁶ has for years employed *Sperminum-Poehl*, in an increasing number of cases, in functional neuroses connected with anæmia and lowered nutrition, and was generally satisfied with the results obtained. In two cases of Graves' disease with severe symptoms of anæmia Prof. Eulenburg observed an especially remarkable increase of the strength and weight after the use of *Sperminum-Poehl*. He began to use the same means too in periodically appearing conditions of depression with uraturia. In several cases the *Sperminum-Poehl* showed a beneficial influence on the duration and the intensity of the attacks. Prof. Eulenburg used *Sperminum-Poehl* especially in those cases in which he could with more or less certainty establish an auto-intoxication of the organism.

Prof. Ewald⁵⁶⁷ employed *Sperminum-Poehl* in a number of severe cases of neurasthenia, in general nervous debility following on anæmia, in decrease of the metabolism, in conditions of depression, and in commencing tabes. Here he certainly met with several unfavourable cases, but generally speaking, he obtained positive results. He advises the continuation of the observations and experiments as to the therapeutic action of *Sperminum-Poehl*, from which he never observed any injurious after-effects—a fact which has been confirmed by all observers.

Prof. Fuerbringer⁵⁶⁸ reports on twenty-two observations of nervous diseases which were made under his direction by Dr. Freyhan in the Friedrichshain Hospital. While in organic diseases (seven cases) no effect whatever was obtained with *Sperminum-Poehl*, in the majority of the cases from the group of functional diseases (fifteen cases), especially in neurasthenia (eight) and hysteria (five), great improvement was observed.

Prof. Mendel⁵⁶⁹ employed *Sperminum-Poehl* in a large number of functional neuroses (hysteria, hypochondriasis, and neurasthenia), and found in many cases a temporary and in some a lasting improvement, especially after continued use of *Sperminum-Poehl* (say from four to six weeks). In one case the effect lasted a whole year. Equally as beneficial an effect from *Sperminum-Poehl* was obtained by Prof. Mendel in anæmia as well as in sclerosis of the cerebral artery and other cerebral symptoms caused by it.

On our title-page we say: "Rational Organotherapy with consideration of Urosemiotics." Unfortunately Urosemiotics like Organotherapy, is little appreciated or understood, although both sciences are in the closest touch with physiology, the daughter of medicine.

Since the epoch-making work of Rudolf Virchow, the whole system of medicine of the present day rests on a cellular-pathological foundation. Unfortunately, however, the cellular-pathological investigation developed almost entirely on the morphological side, not towards the physiological in general, and least of all towards the physiological-chemical side.

Prof. Max Verworn in his article "Die Beziehung der Physiologie zur Biologie und Medizin," refers to his doctrine of the effects of irritation.

According to Verworn, the irritation is a change in the external conditions which influences the condition of a living system existing at the then time. The effects of an irritation find their expression in a qualitative or a quantitative change of the respective vital processes. Now as the disease, according to Verworn, is nothing but life under changed external conditions, that is, life under the influence of irritations, pathology is in the last instance entirely a doctrine of the abnormal action of irritations.

Verworn furnishes in his views an explanation of auto-intoxication. Life under the influence of abnormal irritations also represents life under the conditions of auto-intoxications. Before everything else the physician at the sick-bed will have to ask himself the question which part is primarily affected by the action of the irritation. Does this action consist of an excitation or a paralysis or perhaps a qualitative change of the normal vital processes? How must this change in the affected

part, in consequence of the close correlativeness of all the elements of the body, operate on these or those neighbouring or more remote parts, and how in this way is the whole vital machinery of the organism disturbed ?

Instead of this, says Verworn, there is in the eye of the well-educated modern physician at the sick-bed an image of the microscopical preparation of the affected part, if possible, nicely stained with red or blue nuclei, but he does not consider that the cells which he has before his mind live, and he altogether forgets the chemistry of the healthy and the diseased cell. Here is the place from which the general cellular physiology must start ; here the medical diagnostic must enter into the most intimate relation to the general physiology, if it tends to a further and deeper development.

Nor can therapeutics do without a thorough knowledge of action of the irritation. For therapeutics, in the first place, a fundamental quality of the living substance must be taken into consideration, to which Ewald Herring first called attention. It is the internal "self-steering" of the vital processes. If any irritation has disturbed the equilibrium of the normal metabolism or change of energy, it restores itself on its own account after the cessation of the irritation, provided the action of the irritation has not so far exceeded certain limits that death takes place. The therapeutic task of the physician would be essentially the removal of the damaging action of the irritation. Then the organism will help itself. The most striking proof of the correctness of these views is furnished by the modern experiments for revivification of the organs made by Locke, Kuljabko, Botschareff and others. In these experiments the main object is to remove the abnormal paralysing substances, and not at all to change the morphology of the cells.

The many-sided character of the effects of the Spermin therapy, as before said, is explained as soon as we take into consideration that the decreased textural respiration, that is the auto-intoxication, causes abnormal effects of irritation in very different organs and tissues. By the increase of the processes of oxidation in the Spermin therapy the irritating substances are removed.

For the recognition of disease, that is, life under the influence of abnormal irritations, that is, under changed

external conditions, physiological chemistry in general and the rational urinalysis especially furnish us with the means.

Bouchard, Brouardel, Robin, Arm. Gautier, Charrin and others have pointed to the great significance of the coefficients of the urine. Robin very properly says that the diseases are characterised by a general or localised disturbance of functions of the metabolism, and he lays stress on the fact that most diseases are preceded by a more or less lengthy period in which the disturbances of the functions are curable. Only later, when organic injuries are developed, are they incurable. With reference to this Robin quotes Marey's words, "*La fonction crée l'organe,*" and adds, "*c'est la maladie de la fonction qui crée la lésion de l'organe.*"

In the urinalysis the approach of the disease can be recognised. This, of course, cannot be done with the urinalysis as it is usually performed in most clinics, but with a urinalysis considering the coefficient of urine. Robin says, "*Une bonne analyse d'urine permet de mesurer non seulement les actes généraux des échanges organiques, mais encore les activités particulières de la plupart des organes.*"

We have given ourselves the task of pointing to these co-efficients of urine in such a way as experience has taught us. A thorough discussion of the differential diagnosis of the different auto-intoxications (this question was discussed by Poehl some ten years ago) we shall give in the next volume. At present we only wish to mention that direct experiments showed us that for Organotherapy the coefficients of urine are not only indications for the therapeutic employment of this or that particular preparation, but, and this is just as important, they furnish to the physician a means whereby he may control the therapeutic effect and render an account to what extent the therapeutics employed have influenced, that is, suspended, the external altered relations, which is practically the disease.

Rational Organotherapy in general, and the Spermin therapy especially, are called upon to promote investigation in the field of the auto-intoxications, and, more than this, therapy gives to the physician the means of favourably influencing the symptoms of disease, and in many instances the causes also of disease, without doing harm to the patient.

BIBLIOGRAPHY.

1. A. VON POEHL. "Organo-therapeutic preparations which satisfy the demands of Medicine (Opopreparation)," *Wratsch* (in Russian), 1897, No. 27.

2. BROWN-SEQUARD. "Arch. de Physiologie norm. et pathol." 1889. "Korrespondenz-Blatt d. ärztl." Vereins v. Thüringen. 1889.

3. A. VON POEHL. "On the conditions of the Spermin Essence effect on the Process of Oxidation in the organism in general and in special so far as the nervous system is concerned." *Journal for Medicinal Chemistry and Pharmacy* (Russian).

4. P. F. RICHTER. "Die Organotherapie." Berlin, 1897.

5. ERNST MANGOLD. "Zentralbl. f. Physiologie," Bd. 16, No. 4.

6. HEUBEL. Pflüger's "Arch. f. d. ges. Physiol.," Bd. 45.

7. SCHMULEWITSCH, *cf.* Cyon, *l.c.*

8. CYON. "Zentralblatt f. medicin. Wissensch.," 1870.

9. SCHMIEDEBERG u. BUNGE. "Arch. f. experiment. Pathologie," Bd. vi.

10. LABORDE. "Comptes rendus de la Société de Biologie de Paris," 1890.

11. A. SETSCHENOFF. Pflüger's "Arch. f. d. ges. Physiologie," Bd. 27, 1882.

12. LOCKE. "Zentralbl. f. Physiol.," Bd. 14, 1901.

13. A. KULJABKO. Pflüger's "Arch. f. d. ges. Physiol.," Bd. 90, p. 461, 1902. "Zentralblatt f. Physiologie," Bd. 16. "Comptes rendus de l'Acad. des Sciences de Paris," 1903.

KULJABKO. "Versuche am isolierten Vogelherzen," "Zentralblatt f. Physiol.," Bd. xv., p. 588, 1901; und "Berichte der Kaiserlichen Akademie der Wissenschaften," Bd. xv., 1901, St. Petersburg.

KULJABKO. "Studien über die Wiederbelebung des Herzens," "Arch. f. d. ges. Physiol.," Bd. 90, p. 461, 1902; und "Berichte der Kaiserlichen Akademie," Bd. xvi., 1902.

KULJABKO. "Pharmakologische Untersuchungen am isolierten Herzen." "Berichte der Akademie der Wissensch., St. Petersburg.," Bd. xvi., 1902.

KULJABKO. "Weitere Studien über die Wiederbelebung des Herzens," "Wiederbelebung des menschlichen Herzens Arch. f. d. ges. Physiol.," Bd. 97, p. 539, 1903; und "Berichte der Kaiserlichen Akademie der Wissensch., St. Petersburg.," Bd. xvii., No. 5, 1902. "Zentralbl. f. Physiolog.," Bd. xvii. "Compt. rend. de l'Académie des Sciences de Paris," 1903.

14. MARIE MANASSEÏN. "Wiesner's mikroskopische Untersuch." Wien, 1871.
16. BROWN-SEQUARD. *L.c.* No. 2.
15. PROFESSOR J. PAWLOFF. "Digestive Glands." Translated from the Russian by Dr. Walther.
17. OSTWALD. "Ueber Katalyse," 73. "Naturforscherversammlung in Hamburg," 1901.
18. A. VON POEHL. "Mélanges physiques et chimiques tirés du Bulletin de l'Académie Impériale des Sciences de St. Pétersbourg." Tome xiii., le 22 Avril, 1892.
19. TAKAMINE. "Therap. Gazette," 1901, p. 221.
20. ALDRICH. "American Journ. of Physiol.," 1901, p. 547.
21. A. VON POEHL. "Influence des Agents de catalyse sur le fonctionnement de l'organisme: spermine, cérébrine et chloradrénal." "Compt. rend de l'Académie des Sciences de Paris," 15 Dec. 1902.
22. POEHL. "Ueber die Bedeutung der Katalysatoren für das Leben und die Gesundheit des Organismus im allgemeinen und über Spermin, Cerebrin und Adrenalin im speziellen." "St. Petersburg med. Wochenschr.," 1903, No. 3.
23. A. GAUTIER. "Leçons de chimie biologique." Paris, 1897, p. 197.
24. BOUCHARD. "Leçons sur les auto-intoxications dans les maladies," "Le Gendre." Paris, 1887.
25. POEHL. "Einwirkung des Spermins auf den Stoffumsatz bei Autointoxikationen im allgemeinen und bei harnsaurer Diathese im speziellen." "Zeitschr. f. klin. Med.," Bd. xxvi., Heft. 1, u. 2.
26. HAIG. "Uric acid as a factor in the causation of disease." London, 1902.
27. BOUCHARD. "Leçons sur les auto-intoxications." Paris, 1887.
28. GAUTIER, ARM. "Les toxines microbiennes et animales." Paris, 1896, pp. 282-286; 358-361; 475-477.
29. POEHL. "Zur Erklärung der Wirkung des Spermins als physiologisches Tonikum auf die Autointoxikationen." "Berl. klin. Wochenschr.," 1893, No. 36.
30. POEHL. "D'un rapport entre les oxydations intraorganiques et la production d'énergie cinétique dans l'organisme." "Compt. rend de l'Académie des Sciences de Paris," 24 April, 1899.
31. POEHL. "Ueber das Wesen und die Therapie osmotischer Anomalien in den Körpersäften." "Vortrag gehalten in der St. Petersburg. med. Ges.," 13 Febr. 1901 u. "Journ. f. med. Chem. u. Organother." März 1902, pp. 45-56. "Autointoxikationen, bedingt durch Anomalien der Gewebsatmung u. des osmotischen Druckes, Vortrag" in der "Gesell. deutsch. Naturforscher u. Aerzte zu Karlsbad." 1902. "Journ. f. med. Chem. u. Organoth." März 1903, pp. 75-86.
32. OSTWALD. "Grundriss der allgemeinen Chemie." 1899, III. Aufl. p. 514 bis 521. "Grundlinien der anorganischen Chemie." 1900, pp. 109, 165, 343, 593, 660. "Ueber Katalyse. Vortrag auf der 73. "Naturforscherversammlung in Hamburg." 1901.
33. POEHL. "Die Anwendung von physiologischen Katalysatoren als Arzneimittel." "Vortrag in der Ges. deutsch. Natur-

forscher u. Aerzte in Kassel." September, 1903. "Journ. f. med. Chem. u. Organother." Jan. 1904, p. 75-90p.

34. HAMBURGER. "Osmotischer Druck und Ionenlehre in den medizinischen Wissenschaften." Bd. I. 1902.

35. KOEPE. "Zeitschr. f. physikol. Chem." 1895, p. 260. "Deutsch. Med. Wochenschr." 1895, No. 94. "Arch. f. d. gesamt. Physiol." 1896, p. 67, 1897, pp. 184 u. 492.

36. FÜRST TARCHANOFF. "Biologisch-chemische Untersuchungen der Leuchtbakterien." "Journ. f. Med. Chem. u. Organotherap," 1902, März.

37. POEHL. "Influence des agents de catalyse sur le fonctionnement de l'organisme: Spermine, Cérébrine et Chloradrénal." Extrait du "compte rendu des séances de l'Académie des Sciences de Paris." 15 Dec. 1902.—"Ueber die Bedeutung der Katalysatoren für das Leben und die Gesundheit des Organismus im allgemeinen und über Spermin, Cerebrin und Adrenal im speziellen." "St. Petersburg. Med. Wochenschr." 1903, Nr. 9.

38. N. O. SIEBER und E. G. SCHUMOWA-SIMANOWSKAJA. "Ges. Russ. Aerzte." 22 Jan. 1904.

39. POEHL. "Über die Bedeutung der Katalysatoren für das Leben und die Gesundheit des Organismus im allgemeinen und über Spermin, Cerebrine und Adrenalchlorid im speziellen." "St. Petersburg. Med. Wochenschr." 1903, Nr. 3.

40. PURINTON, cf. Poehl. "Journ. f. Med. Chem. u. Organotherap." 1903, März, p. 12.

41. MOORE, cf. Poehl. "Journ. f. Med. Chem. u. Organotherap." 1903, März, p. 12.

42. POEHL. "Die neuesten Ergebnisse über die chemischen Prozesse des Lebens in Beziehung zur Frage über die Bedeutung des Adrenalchlorid." "Vortrag. in der St. Petersburg. Med. Ges." 17 Dec. 1902. "Journ. f. Med. Chem. u. Organotherap." März 1903, p. 125.

43. POEHL, l.c. No. 33.

44. POEHL, l.c. No. 39.

45. LION. "Berl. Klin. Wochenschr." 1903, Nr. 1. und "Deutsch. Med. Wochenschr." 1902, No. 50. "Journ. f. Med. Chem. u. Organotherap." 1902, März, p. 9-29, und 1903, März, pp. 29-46.

46. STANGE. "St. Petersburg. Med. Wochenschr." 1902, und "Journ. f. Med. Chem. u. Organotherap." 1903, März, p. 91.

47. EULENBURG. "Deutsch. Med. Wochenschrift." 1902, No. 50. "Journ. f. Med. Chem. und Organotherap." 1903, März, p. 45.

48. SIEBER und SIMANOWSKAJA, l.c. No. 38.

49. v. EICHWALD. "Allgemeine Therapie," p. 15.

50. v. HIRSCH. "Beitrag zur Organotherapie." "Sperminum-Poehl. "St. Petersburg. Med. Wochenschr." 1897, No. 7. "Contribution à l'Organothérapie et à l'étude de la Spermine-Poehl," "La Tribune Médic.," 1897.

51. POEHL. "Zur Erklärung der Wirkung des Spermins als physiologisches Tonikum auf die Autointoxikationen." "Berl. Klin. Wochenschr." 1893, No. 36.

52. ZUELZER. "Lehrbuch der Harnanalyse," 1880.

53. POEHL. "Vorlesungen über Harnanalysen." 1895-96, in d. "Kais. Klin. Institut. St. Petersburg," 1897.

54. ALB. ROBIN. "Bulletin de la Société médicale des hôpitaux Fév." 1886 u. cf. Vieillard, "L'urine humaine," 1897, p. 69.
55. BOUCHARD, cf. Vieillard. "L'urine humaine," 1889.
56. NEUMEISTER. "Lehrbuch der physiol. Chem." 1895, T. ii, p. 231.
57. v. SCHROEDER. "Arch. f. expr. Pathol." xv., p. 364. u. cf. Neubauer & Vogel, *l.c.*, ii. p. III.
58. HOPPE-SEYLER. "Handbuchh d. physiolog. u. pathol.-chemischen Analyse." 1893, p. 343.
59. POEHL. "Tageblatt d. 60. Versammlung d. Naturforsch. u. Aerzte in Wiesbaden," 1887, No. 5. "Die Eigenschaft des Harnes der Syphilitiker und Beiträge zur Frage über die Immunität der Tiere gegenüber der Syphilis."
60. POEHL. "Berl. klin. Wochenschr." 1893, No. 36.
61. BARON v. OEFELE. "Koprologie," 1904.
- 62 u. 63. ROBIN, *l.c.* No. 54.
64. v. NOORDEN. "Pathol. d. Stoffwechsels," p. 315.
65. R. HUGUET. "Notes d'urologie;" u. cf. Vieillard, "L'urine humaine," p. go.
66. BAYRAC. "Thèse de Lyon," 1884; u. cf. Vieillard, "L'urine humaine," p. 90.
67. BOUCHARD, cf. Vieillard. "L'urine humaine," p. 89.
68. BOUCHARD. "Maladies par le ralentissement de la nutrition." p. 127 (cf. Vieillard. "L'urine humaine," pp. 94-95). "L'azote total mesure l'activité de la désassimilation des albuminoïdes tandis que l'azote de l'urée est en rapport avec leur degré d'oxydation, ou si l'on préfère avec l'énergie comburante. Il faut se rappeler que parmi les produits azotés de la désassimilation, l'urée est le seul qui ne puisse pas atteindre, dans l'organisme, un degré plus élevé d'oxydation; tandis que l'acide urique et les autres corps azotés ne réalisent pas au maximum l'oxydation des produits azotés."
69. PFLÜGER UND BOHLAND. Pflüger's "Arch. Bd." 38, p. 575, u. cf. Neumister, p. 234.
70. POEHL. "Verh. d. Kongr. für innere Medizin." 1896, p. 84.
- 71 u. 72. POEHL. "Journ. f. med. Chem. u. Pharm.," 1892, No. 1, pp. 46-55.
73. NEUMEISTER. "Lehrb. d. phys. Chem." ii. Teil, p. 226.
74. POEHL. "Spermintheorie," p. 75.
75. HINTEREGGER. Ber. d. d. chem. Ges. 12, 1879, p. 1619, bis 1626, u. cf. Ladenburg's "Handw. d. Chem.," iii. p. 303.
76. OTT, *l.c.* NEUBAUER u. VOGEL, p. 15.
77. HAUSMANN. "Zeitschr. f. klin. Medizin," Bd. xxx. 1896, Heft. 3 u. 4.
78. JOULIE. "Urologie pratique et thérapeutique nouvelle." Paris, 1901.
79. BOUCHARD. "Traité de pathologie générale." Paris, 1900.
80. RICHTER. "Zeitschr. f. klin. Med.," Bd. 27, Heft. 3 u. 4.
81. POEHL. "Spermintheorie." 1898.
82. BOUCHARD. "Maladies par ralentissement de la nutrition." Paris 1885.
83. SENATOR. "Die Autointoxikation und ihre Behandlung" "Die deutsch. Klinik," Prof. von Leyden u. Prof. Klemperer 2. Vorlesung, p. 32; Berlin, 1901.

84. P. F. RICHTER. "Zeitschr. f. klin. Med.," Bd. 27, Heft. 3 u. 4.
85. SENATOR, *cf.* Richter, *l.c.*
86. VON MERSHEJEWSKY, *cf.* Poehl. "Vorlesungen über Harnanalysen, 1895-96, geh. in. d. Kais. klin. Institut. St. Petersburg," 1897.
87. ZUELZER. "Lehrbuch der Harnanalyse." 1880.
88. MAIRET. "C. r. d. l. Soc. de Biol.," 5 et 12 juillet, 1884.
89. MAIRET, *cf.* Vieillard. "Sémiologie urinaire," p. 138.
90. VIEILLARD. "Urine humaine." Paris, 1898; "Sémiologie urinaire," 1901.
91. ARM. GAUTIER. "Chimie biologique."
92. KÜHNE. "Ber. d. d. chem. Ges." 1875, p. 206.
93. NENCKY. *Ibid.* 1875, p. 336, u. f.
94. JAFFÉ. "Zentralb. f. med. Wiss.," Bd. 10, Heft. 2, pp. 481, 497, 1872.
95. E. SALKOWSKI. "Ber. d. d. chem. Ges." 1876, Bd. ix., pp. 138, u. 408.
96. BAUMANN UND BRIEGER. "Zeitschr. f. phys. Chem." 1888, p. 544.
97. SENATOR. "Zentralbl. f. med. Wiss." 1877, p. 357.
98. HAMMERSTEN. "Lehrb. d. phys. Chem." 1891, p. 391.
99. E. SALKOWSKI. Virchow's "Arch." 1875, Bd. 58, p. 472.
100. LÉPINE. "Révue de Médec." 1881, p. 27.
101. KUNKEL, *cf.* Neubauer und Vogel. "Analyse des Harns." 1890, p. 11.
102. REALE UND VELARDI. "Jahresb. d. Tier-Chem." 1896, p. 326.
103. VOIRIN. "Variations physiologiques et pathologiques du soufre urinaire." Nancy, 1894.
104. REALE UND VELARDI. *L.c.*, No. 102.
105. STADTHAGEN, *cf.* Neubauer und Vogel, *l.c.* p. 12.
106. STÄDELER. "Annal. d. Chem. u. Pharm.," 1851, p. 17.
107. BRIEGER. "Zeitschr. f. phys. Chem." 1880, p. 207.
108. BAUMANN. *Ibid.* 1882, p. 187.
109. KESSLER UND PENNY. *Ibid.* 1893, p. 117.
110. SALKOWSKI. "Ber. d. d. chem. Ges.," Bd. ix., 1895.
111. BRIEGER. "Zeitschr. f. phys. Chem." ii., p. 256.
112. BLENDERMANN. *Ibid.* 1882, p. 240.
- 113 u. 114. POEHL. "Harnanalyse und die Bestimmung der Darmfäulnis auf Grund der Harnanalyse." "Journ. f. med. Chem. u. Organother." 1898, Feb., p. 236.
115. ALBU. "Ueber den Einfluss verschiedener Nährmethoden auf die Darmfäulnis, Vortrag gehalten im Verein f. innere Medizin." Berlin, 1897, 12 April.
116. HAMBURGER. "Die osmotische Spannkraft in den medizinischen Wissenschaften." "Virch. Arch." 1895, p. 503, bis 523.
117. VON KORANYI. "Physiologische u. klinische Untersuchungen über den osmotischen Druck tierischer Flüssigkeiten." "Zeitschr. f. klin. Med." 1897, Bd. 33, Heft. 1 u. 3.
118. POEHL. "D'un rapport entre les oxydations intraorganiques et la production d'énergie cinétique dans l'organisme." "Comptes rendus de l'Académie des Sciences." Paris, 1899, 24 avril.
119. VON KORANYI. "Offenbar zieht v. K. nur die Mineralsalze

und Extraktionsstoffe in Betracht und bringt die Eiweisskörper als nicht gelöste, sondern zur gequollene Körper nicht in Bedeutung, was bei Beurteilung von osmotischer Eigenschaft entschieden zweckmässig ist."

120. POEHL. "Der osmotische Druck der Körpersäfte in seiner Beziehung zur Entstehung und Beseitigung von Krankheitszuständen." "Zeitschr. f. diät. u. physik. Therapie," 1900-1901, Bd. iv., Heft. 1.

121. VON KORANYI. "Zeitschr. für klin. Med." 1899, Bd. 33, Heft 1, p. 4, cf. Poehl, *l.c.*

122. POEHL, *l.c.*

123. POEHL. "D'un rapport entre les oxydations intraorganiques et la production d'énergie cinétique dans l'organisme." "Compt. rend. d. l'Académie des Sciences." Paris, 24 avril, 1899.

124. POEHL. "Ueber die Anwesenheit und Therapie der osmotischen Anomalien in den Körpersäften," "Vortrag geh. in d. St. Petersburg. med. Ges." 13 Febr. 1901.

125. B. BRASCH. "Die Anwendung der physikalischen Chemie auf die Physiologie und Pathologie."

126. ZICKEL. "Lehrbuch der klin. Osmologie," 1902.

127. POSNER. "Die Florence'sche Reaktion nebst Bemerkungen über Spermin." "Berl. klin. Wochenschr.," 1897, No. 28.

128. A. BÖTTCHER. "Virchow's Arch." 32, p. 525.

129. SCHREINER. "Annal. d. Chem." 194, p. 68.

130. LADENBURG UND ABEL. "Ber. d. d. chem. Ges." 1888, p. 758.

131. KOBERT. "Pharm. Zentralhalle," 1889, p. 736.

132. POEHL. "Minutes of the St. Petersburg Medical Society," 1890 (Russian).

133. POEHL. "Ber. d. d. chem. Ges." 1891, xxiv., Heft. 3.

134. MENDELEJEFF. Wratsch (Russian), 1890, p. 1106, and *St. Petersburg Medical Weekly Gazette*, 1890.

135. POEHL. "Russ. chem. Ges." 7 Febr. 1891. "Protokolle und Mitteilungen der Versammlung der St. Petersburg. med. Ges." 26 Febr. 1891; "Ber. d. d. chem. Ges." 1891, p. 359, "Berl. Klin. Woche," 1891, No. 39.

136. SCHREINER'S Formel für das Platindoppelsalz = $(C^2H^5N.HCl)^2 PtCl^4$.

137. POEHL. "Die Frage, ob wir es mit einer Polymere von $C^5H^{14}N^{12}$ zu tun haben, sowie weitere Untersuchungen über die Chemie des Spermins, behält er sich vor."

138. J. SIEBERT. "Ber. d. d. chem. Ges." 1890, 23, p. 336.

139. W. MAJERT UND ALBERT SCHMIDT. "Ber. d. d. chem. Ges." 1881.

140. A. W. VON HOFFMANN. "Chem. Zentralbl.," 1891, 1, p. 83.

141. POEHL. *St. Petersburg Medical Weekly Gazette*, No. 13, 1886; "Practical Medicine," 1887. "Asepsis and Antisepsis in the service of Pharmaceutical Practice" (Russian).

142. MAJERT UND SCHMIDT. "Ber. d. d. chem. Ges." 1890, p. 2718.

143. POEHL. "Der Ersatz der intravenösen Kochsalzinfusionen, durch Klysman aus künstlicher, physiologischer Salzlösung." "Verhandlung des Kongresses für innere Medizin." Bd. xx., 1902, p. 71.

144. HERM. HAGER. "Pharmaz Post," 1891, p. 369.

145. MERK. "Pharmaz. Zeitschr. f. Russl." 1890, p. 248.

146. MAJERT UND SCHMIDT. "Ber. d. d. chem. Ges." 1890, p. 2718.

147. SCHREINER. "Liebig's Annalen d. Chem.," Bd. 194, p. 76.
148. POSNER. "Vortrag im Berl. Huteland-Verein," d. 3 Jun. 1897. "Berl. klin. Wochenschr." 1897, No. 36. *Journal f. med. Chem. und Pharm.* (russ.), 1898, p. 192.
149. FLORENCE. "Du sperme et des taches de sperme en médecine legale." "Archive d'antropologie criminelle," T. x. et xi.
150. POEHL. *Journal für med. Chem und Pharm.* (russ.) 1897, p. 71.
151. WYATT JOHNSTON. "Bericht gehalten. im med. Verein in Massachuset," 3 Oct. 1896. *Journal f. med. Chem. und Pharm.* 1897, p. 66.
152. W. F. WHIBNEY. "Bericht geh. in med. Verein in Massachuset," 3 Febr. 1897. *Journal f. med. Chem. und Pharm.*, 1897, p. 76.
153. MAX RICHTER. "Wien klin. Wochenschr.," 1897, No. 24.
154. N. BOCARIUS. "Jahresb. d. Tierchem.," 1902, p. 576 und "Zeitschr. f. Physiol. Chem." 34, pp. 339-346.
155. P. FÜRBRINGER. "Zeitschr. f. klin. Med.," iii., pp. 287-316. "Jahresb. d. Tierchem.," 1881, p. 351.
156. POEHL. "Der Nachweis des Spermins in verschiedenen Drüsen des tierischen Organismus und die chemische Zusammensetzung des Brown-Séquard'schen Heilmittels." *Deutsch. med. Wochenschr.* 1892, No. 49.
157. CHARCOT ET ROBIN. "Compt. rend. de la Soc. de Biologie," 1853, p. 49.
158. FÖRSTER. "Abt. d. mikrosk. Anatomie." 1854, Taf. xxxiii., Fig. 4 und p. 67.
159. HARTING. "Das Mikroskop. Braunschweig," 1859, p. 458.
- 160 u. 161. CHARCOT UND VULPIAN. "Gaz. hebdom." 1860, p. 47.
162. WHITE. *Boston med. and surgcon Journ.*, Nov. 28, 1861, und "Brit. and For. Med.-chir. Review," Apr. 1862, p. 532.
163. WAGNER. "Arch. d. Heilkunde," 3, p. 379.
164. FRIEDRICH. "Arch. f. path. Anat., Physiol. u. kl. Med." 30, p. 382.
165. HUPPERT. "Schmidt's Jahrb.," 124, 147.
166. BÖTTCHER. "Arch. f. path. Anat., Physiol. u. kl. Med.," 32, p. 525.
167. KÜHNE. "Lehrb. d. physiol. Chem.," 1868, p. 558.
168. HOPPE-SEYLER. "Handb. d. Physiol. u. pathologische-mischen Analyse," 1870, p. 191.
169. NEUMANN. "Arch. f. mikrosk. Anat.," 2, p. 507.
170. VON LEYDEN. "Arch. f. pathol. Anat." etc., 54, pp. 324 u. 346.
171. SALKOWSKI, a. a. O. S. 344.
172. LAUENSTEIN. "Deutsch. Arch. f. kl. Med.," 1876, 18, p. 122.
173. ZENKER. "Deutsch. Arch. f. klin. Med." 1876, 18, p. 122.
174. SCHREINER. "Ann. d. Chem." 1878, 194, p. 68.
175. FÜRBRINGER. "Deutsch. Med. Wochenschr.," 1891, pp. 1028, u. 1059, 1892 p. 102.
176. P. GUTTMANN. "Deutsch. Med. Wochenschr." 1892, p. 102.
177. POEHL. "Melanges physiques et chimiques; tirés du Bulletin de l'Académie Impériale des Sciences de St. Petersbourg." T. xiii. l.c. 2 Avr. 1892.

178. POEHL. "Bulletin de l'Académie Impériale des Sciences de St. Petersburg." Beilage zum T. lxii, No. 2, 1892.
179. POEHL. "Action physiolog. de la spermine. Interprétation de ses effets sur l'organisme." "Compt. rend. des séances de l'Académie des Sciences." Paris, 11 juillet, 1892.
180. DUCLAUX, *ibid.*, 18 Juillet, 1892.
181. POEHL. "Du rôle de la spermine dans les oxydations intra-organiques." "Compt. rend. des séances de l'Académie des Sciences." Paris, 10 Oct. 1892.
- 182 u. 183. POEHL. "Bulletin de l'Académie Impériale des Sciences de St. Petersburg." Beilage. No. 2, zum T. xxi. 1892.
184. v. JAKSCH. "Klin. Diagnostik," II. Aufl., 1889, p. 4.
185. POEHL. "Deutsch. Med. Wochenschr.," 1895, p. 475. Journal f. Med. Chem. u. Pharm., 1895, p. 316.
186. SCHMIEDEBERG. "Arch. f. experim. Pathol. u. Pharm." 1881.
187. RÖHMANN und SPITZER. "Ueber Oxydationswirkung tierischer Gewebe. Ber. d. d. chem. Gesell." 1894, p. 567.
188. POEHL. "Ueber die Bedeutung der Katalysatoren für das Leben und die Gesundheit des Organismus im allgemeinen und über Spermin, Cerebrin und Adrenal im speziellen." "St. Petersb. Med. Wochenschr.," No. 9, 1903.
189. COHN. "Zur Frage von der Theorie der Sperminwirkung." 1894, Sept.
190. SALKOWSKI. "Zeitschr. f. physiol. Chem.," 7, 1882.
191. ABELOUS u. BIARNES. "Arch. f. physiol. Chem.," 1894.
192. JAKOBY. "Zeitschr. f. physiol. Chem.," 1900, 30.
193. ROSELL. "Dissertation (bei Hofmeister)," Strassburg, 1901.
194. BOURQUELOT. "Compt. rend. de la Société de Biolog.," 1896, p. 379.
195. BERTRAND, *cf.* Poehl. "Spermintheorie," p. 58, 1898.
196. MEDWEDJEFF. "Pflüg. Arch.," 1896, 65, p. 249.
197. GAUTIER. "Les Toxines microbiennes et animales." Paris, 1897.
198. GAUTIER. "Cours et Chimie biologique," p. 208.
199. BOUCHARD. "Recherches experimentales sur la toxicité des urines normales." "Société de Biologie," 1884. "Leçons sur les autointoxications dans les maladies." Paris, 1887.
200. GAUTIER. "Les toxines microbiennes et animales." Paris, 1887, p. 382-386; 358-361; 475-477.
201. GAUTIER u. LANDO-LANDI. "Arch. de Physiol. de Brown-Séquard," 1893, Janv.
202. BOUCHARD, s. No. 199.
203. HALLIBURTON, W. D. "The proteids of nervous tissues." "Journ. of Physiolog.," xv., pp. 90-107.
204. AFANASJEFF, *cf.* Ranke. "Grundzüge der Physiol.," 1881, p. 729.
205. LIEBIG. "Annal. d. Chem. u. Pharm.," Bd. 62, 1847, p. 326.
206. ENGELHARDT. "Annal. d. Chem. u. Pharm.," Bd. 65, 1848, p. 359.
207. WISLINCENUS. "Annal. d. Chem. u. Pharm.," 1873, p. 302.

208. HEINTZ. "Annal. d. Chem. u. Pharm.," 1871, p. 320.
209. DU BOIS-RAYMOND. "Ber. d. Berl. Akademie," 1859, p. 288.
210. ASTASCHEWSKY. "Z. f. physiol. Chem.," 1880, p. 397.
211. W. COHNSTEIN. "Ueber Aenderung der Alkaleszenz durch Muskelarbeit." "Virch. Arch.," 1892, p. 332.
212. Vergl. namentlich auch RÖHMANN. "Ueber die Reaktion der quergestreiften Muskeln." "Pflüger's Arch.," Bd. 39, 1886, p. 425.
213. MARCUSE. "Ueber die Bildung von Milchsäure bei der Tätigkeit des Muskels, etc." "Pflüger's Arch.," Bd. 39, 1886, p. 425.
214. WERTHER. "Pflüger's Arch.," Bd. 46, 1889, p. 63.
215. DU BOIS-RAYMOND. "A. u. O.," p. 31.
216. GÖTSCHLICH. "Beiträge zur Kenntnis der Säurebildung und des Stoffumsatzes im Muskel." Pflüger's "Arch.," Bd. 56, 1894, p. 363.
217. DRESER. "Ein Vorlesungsversuch betreffend die Säurebildung bei der Muskeltätigkeit." "Zentralbl. f. Physiol.," Bd. i., 1887, p. 195.
218. BERZELIUS, Siehe G. G. LEHMANN. "Lehrbuch der physiol. Chem.," Leipzig, 1860, p. 103.
219. v. BIBRA, cf. Müller. "Ann. d. Chem. u. Pharm.," Bd. 103, 1857, p. 152.
220. POEHL. Paris Congrès international de médecine, 1900 und "Die Nervenüberreizungen als Ursache von Autointoxikationen," "Deutsch. Med. Wochenschr.," No. 46. 1901.
221. POEHL. "Zur Erklärung der Wirkung des Spermins als physiologisches Tonicum auf die Autointoxikationen," "Berl. Klin. Wochenschr.," 1893, No. 36.
222. POEHL hat den Übergang des amorphon Sperminphosphates in das kristallinische nicht nur beobachtet ("Berl. Klin. Wochenschr.," 1893, No. 36), sondern es ist ihm auch gelungen, denselben in einer Serie von Mikrophotogrammen zu fixieren.
223. F. CHVOSTEK. "Zentralbl. f. klin. Mediz.," 1893, 14, pp. 329-334. "Jahresb. d. Tierchem.," 1893, p. 10.
224. WALTER. "Jahresb. d. Tierchem.," vii. p. 141.
225. POEHL. "Einwirkung des Spermins auf den Stoffumsatz bei Autointoxikationen im allgemeinen u. bei harnsaurer Diathese im speziellen." "Zeitschr. f. klin. Med." Bd. xxvi., Heft 1 u. 2.
226. HORBACZEWSKI, cf. Neumeister. ii, l.c., p. 235.
227. HORBACZEWSKI. "Jahresb. d. Tierchem.," 1892, p. 429.
228. HAIG. "Uric Acid as a factor in the causation of Disease." London.
229. HEBTER u. E. SCHNIDT. "Jahresb. d. Tierchem.," 1892, p. 203.
230. RUDEL. "Jahresb. d. Tierchem.," 1892, p. 199.
231. v. LEYDEN. "Deutsch. med. Wochenschr.," 1891, No. 38.
232. v. ROSSI, s. Poehl. "Spermintheorie," p. 204, u. "Journ. f. med. Chem. u. Pharm." 1893, Dec. p. 347 u. 1894. Sept. p. 154.
233. v. ROSSI u. GRETSCHANINOFF, "Journ. f. med. Chem. u. Pharm." 1894, Sept. p. 155 u. 158, cf. Poehl. "Spermintheorie," p. 204.
234. FLEROFF u. GRETSCHANINOFF. "Journ. f. Med. Chem. u. Pharm." 1894, Sept. p. 155 u. cf. POEHL, "Spermintheorie," p. 205.

235. GRETSCHANINOFF, *cf.* Poehl. "Spermintheorie," p. 205, u. "Journ. f. Med. Chem. u. Pharm." 1895, Sept. p. 155.
236. AFANASJEFF u. SCHAPIRO. "Journ. f. Med. Chem. u. Pharm." 1894, Sept. p. 158 u. 159. u. *cf.* Poehl. "Spermintheorie," p. 197.
237. PROCHOROFF. "Journ. f. Med. Chem. u. Pharm." 1894, Sept. p. 159. *cf.* Poehl. "Spermintheorie," p. 197.
238. v. ROSSI, *cf.* Poehl. "Spermintheorie," pp. 122-125.
239. COHN, *cf.* Poehl. "Spermintheorie," pp. 148-149.
240. SCHULIN. "Journ. f. Med. Chem. u. Organotherapie." 1902, März, pp. 89-94.
241. PODKOPAJEFF. "Journ. f. Med. Chem. u. Pharm." 1894, März u. Dec. *cf.* Poehl. "Spermintheorie," pp. 173-177.
242. PROCHOROFF. *cf.* Poehl. "Spermintherapie," pp. 152-153.
243. v. ROSSI u. GRETSCHANINOFF, *l.c.* No. 233.
244. FLEROFF u. GRETSCHANINOFF, *l.c.* No. 234.
245. WICHERT, *cf.* Poehl. "Spermintheorie," p. 148.
246. ROSSI, *l.c.* 238.
247. ULRICH, *cf.* Poehl. "Spermintheorie," pp. 152-153. "Journ. f. Med. Chem. u. Pharm." 1894, Sept. p. 150.
248. PROCHOROFF, *l. c.* No. 242.
249. v. ROSSI, *cf.* Poehl. "Spermintheorie," pp. 122-123.
250. HILTEBRANDT, *cf.* Poehl. "Spermintheorie." pp. 146-147.
251. ROMANOWSKI, *cf.* Poehl. "Der osmotische Druck der Körpersäfte in seiner Beziehung zur Entstehung u. Beseitigung von Krankheitszuständen." Wratsch. No. 34. 1899.
252. RICHTER. "Zeitschr. f. klin. Med." Bd. 27, Heft 3 u. 4.
253. TARCHANOFF. "Report of the Russian Medical Society in St. Petersburg." Fifty-seventh Annual Report, 1891, No. 4, p. 23. Also "Berlin klin. Wochenschr." 1891, No. 40.
254. KONDRATJEFF. "Journ. f. Med. Chem. u. Pharm.," 1896, Bd. 13 n. 14, p. 628.
255. TARCHANOFF. "Journ. f. Med. Chem. n. Pharm.," 1896, No. 13 u. 14, pp. 737-747.
256. POEHL. "Die Eigenschaften des Harnes der Syphilitiker und Beiträge zur Frage über die Immunität der Tiere gegenüber der Syphilis. Tagebl. d. Versamml. deutscher Aerzte u. Naturforscher in Wiesbaden," 1887, Nr. 5. "Einwirkung des Spermins auf den Stoffumsatz bei Autointoxikationen im allgemeinen und bei harnsaurer Diathese im speziellen." XI. intern. med. Kongr., Rom. 30. März, 1894; *cf.* "Zeitschr. f. klin. Mediz." xxvi, Heft 1 u. 2. "Russ. Journ. f. Med. Chem. u. Pharm.," 1894, pp. 141-194.
257. POEHL. "Die Immunitäts- u. Immunisations-theorie von biologisch-chemischem Standpunkt betrachtet." "Die Kaiserl. russ. Akademie d. Wissensch." vom Akademiker Prof. Dr. N. Beketoff mitgeteilt am 7-29, Nov. 1894. "Deutsch. Med. Wochenschr." 1895, Nr. 6. "Wratsch," 1894, Nr. 49.
258. POEHL. XI. Intern. Med. Kongr. Rom., 30 März, 1894, "Zeitschr. f. klin. Med." xxvi., 1. u. Heft, p. 136. "Russ. Journ. f. Med. Chem. u. Pharm.," 1894, pp. 141-194.
259. POEHL. "Die Immunitäts- u. Immunisations-theorie von biologisch-chemischem Standpunkt aus betrachtet." *l. c.* No. 257.
260. HORBACZEWSKY. "Jahresb. d. Tierchem.," 1892, p. 17.
261. BREDIG. "Die Elemente der chem. Kenitik mit besonderer

- Berücksichtigung der Katalyse u. der Fermente." "Wirkung und Ergebnisse der Physiologie," Bd. i., Asher u. Spiro, 1892, p. 206.
262. POEHL, s. No. 258.
263. "General Pathology."
264. CHARRIN u. ROGER. "Sem. Médic.," 1892, p. 268.
265. POEHL. "Die Nervenüberreizung als Ursache von Auto-intoxikationen." "Deut. Med. Wochenschr.," 1901, No. 46.
266. BEHRING, cf. Eulenburg's "Encyclop. Jahrb.," 1894, p. 323.
267. v. FODOR. VIII. intern. Kongr. f. Hygiene in Budapest, 1894, cf. "Allg. Med. Zentr.-Zeitg.," 1894, No. 83, p. 969.
268. v. FODOR u. RIFGLER. "Jahresb. p. Tierchem.," 1897, p. 220.
269. BUCHNER. "VIII. intern. Kongr. für Hygiene," 1894.
270. WASSERMANN. "Tagebl. d. Naturforscherversamml.," p. 187.
271. S. S. BOTKIN. "Deutsch. med. Wochenschr.," 1892, No. 15.
- "Berl. klin. Wochenschr.," 1892, Nr. 19.
272. v. BUNGE. "Lehrb. d. physiol. u. patholog. Chem.," 1894, p. 231.
273. ARM. GAUTIER. "La chimie de la cellule vivante."
274. HANKIN, KANTHACK u. HARDY, cf. Metschnikoff-Podwysotszki, s. No. 263.
275. VON LEYDEN. "Deutsch. med. Wochenschr.," 1892, No. 38.
276. POEHL. "Deutsch. med. Wochenschr.," 1892, No. 49.
277. POEHL. "Ber d. deutsch. chem. Ges.," 1886, Bd. xix., p. 1159. Petri "Arbeiten aus d. Kaisl. Gesundheitsamt," 1890, Bd. vi., p. 1-42.
278. POEHL. Vortrag im Verein "für innere Medizin," Berlin, 30 Mai, 1895. "Deutsch. medicin. Wochenschr.," 1895, No. 30, u. 31.
279. SENATOR. "Deutsch. med. Wochenschr.," 1895, No. 31.
280. G. EPIFANOFF. "Botkin's Journal" (Russ.), No. 30; "Journ. f. med. Chem. u. Pharm." (Russ.), 1895, Nos. 10 u. 11, p. 293-298.
281. LOEWY u. RICHTER. "Deutsch. med. Wochenschr.," 1895, No. 15.
282. LOEWY u. RICHTER. "Zur Biologie der Leukocyten." "Virchow's Arch.," 151, Bd. 1898.
283. LOEWY u. RICHTER. "Virchow's Arch.," Bd. 151, 1898, p. 234.
284. S. S. BOTKIN. "Deutsch. med. Wochenschr.," 1892, No. 15, "Berl. klin. Wochenschr.," 1892, No. 19.
285. HAHN. "Arch. f. Hygiene," 1894.
286. CARO u. STRAUSS. "Zeitschr. f. klin. Med.," 1895.
287. LOEWIT. "Allgem. Patholog. des Fiebers," Jena, 1896.
288. LOEWIT. "Zeigler's Beiträge," 1897.
289. MINKOWSKI. "Ueber Leukämie u. Leukocytose," XVII. Kongr. f. inn. Med., 1899, p. 184.
- 290 u. 291. Vergl. POEHL. "Spermintheorie," St. Petersburg, 1898, p. 113.
- 292 u. 293. *Ibid.* 114.
294. Die Literatur über diesen Gegenstand s. bei NEUMEISTER, "Lehrbuch der physiol. Chem.," 2 Aufl.
295. MINKOWSKI. XVII. Kongress für innere Medizin, 1904.

296. KLEMPERER. "Versaml. f. Naturforsch. u. Aertze zu Kassel," 1903.
297. ARGUTINSKY. "Pflüger's Arch.," Bd. 46, 1890, p. 594.
298. NEUMEISTER. "Lehrbuch d. Physiol. Chem.," ii., p. 94.
299. TICHBORN. "Zentralbl. f. med. Wissensch.," 1888, p. 106.
300. KAST. "Zeitschr. f. physiol. Chem.," 1887, p. 505.
301. TARCHANOFF. "Russ. Journ. f. med. Chem. u. Organotherapie," 1902, März, p. 69.
302. POEHL. "Ber. d. d. chem. Gesell.," 1886, Bd. xix., p. 1159, etc.
303. DNNHAM. "Zeitschr. f. Hyg.," 1887, p. 337.
304. BUJWID. *Ibid.* p. 52.
305. BRIEGER. "Deutsch. med. Wochenschr.," 1887, p. 303, Virchow's "Arch.," 1887, p. 614.
306. E. SALKOWSKI. "Virchow's Arch.," 1887, p. 336.
307. IADASSOHN. "Breslauer ärzt. Zeitschr.," 1887, Nos. 16, u. 17.
308. ZÄSLEIN. "Deutsch. med. Zeitsch.," 1887, No. 72.
309. PETRI. "Arbeiten aus d. Kais. Gesundheitsamt," 1890, Bd. vi., Heft. 1, pp. 1-42.
310. MARINO-ZUCO u. U. DUTTO. "Jahresb. d. Tierchem.," 1892, Bd. 22, p. 548.
311. MARINO-ZUCO u. C. MARTINI. "Jahresb. d. Tierchem.," 1895, Bd. 25, p. 124.
312. MARINO-ZUCO. "Jahresb. d. Tierchem.," 1894, Bd. 24, p. 181.
313. MOTT u. HALLIBURTON. "Jahresb. d. Tierchem.," 1898, Bd. 28, p. 162.
314. LIEBREICH. "Ann. chem. Pharm.," 1865, Bd. 29, p. 134.
315. DIAKONOW. "Med. chem. Untersuchungen von Hoppe-Seyler," 1867, H. 2, p. 221.
316. GULEWITSCH. "Zeitschr. f. physiol. Chem.," 1899, Bd. 27, p. 50.
317. GAUTIER. "Les toxines microbiennes et animales," 1896, p. 120, et 221.
318. MOTT u. HALLIBURTON. "Jahresb. d. Tierchem.," 1899, Bd. 29, p. 95.
319. GAUTIER. "Die Arzneimittel"-Synthese auf Grundlage der Beziehung zwischen chem. Aufbau u. Wirkung von Dr. S. Fränkel," p. 92 u. 247.
320. LOEW u. EHRLICH. "Jahresb. d. Tierchem.," 1892, Bd. 22, p. 247.
321. LIEBREICH. "Ber. d. d. chem. Ges.," 2, p. 12.
322. MARINO-ZUCO u. DUTTO. "Jahresb. d. Tierchem.," 1892, Bd. 22, p. 548.
323. BOINET. "Jahresb. d. Tierchem.," 1896, Bd. 26, p. 525.
324. POLIMANTI. "Jahresb. d. Tierchem.," 1896, Bd. 26, p. 559.
325. MOTT u. HALLIBURTON. "Jahresb. d. Tierchem.," 1897, Bd. 27, p. 102.
326. BEATTIE NESBITT. "Jahresb. d. Tierchem.," 1899, Bd. 29, p. 386.
327. DELLA TORRE. "Jahresb. d. Tierchem.," 1900, Bd. 30, p. 852.

328. Prof. KOBERT u. Dr. med. H. CRAMER. "Ueber den Entgiftungskasten," "Zeitschr. für Krankenpflege," No. 6, 1903.

329. ROBIN u. BARDET. "Traitement des empoisonnements divers," Paris, 1895.

330. KIONKA. "Allgemeine Therapie der Intoxikationen und Autointoxikationen." "Lehrbuch der allg. Therapie und der therapeutischen Methodik." 1899.

331. KAKOWSKI. "Ueber den Einfluss verschiedener Substanzen auf das isolirte Herz Kalt- u. Warmblüter." Dissertation aus dem pharmakol. Laboratorium von Prof. Kobert in Rostock, 1904.

332. FINKELSTEIN. "Journ. f. med. Chem. u. Pharm." (russ.) 1892, Dez. pp. 56-63.

333. PODKOPAJEFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 197-208, u. Dez., pp. 421-434.

334. PANTSCHENKO. "Journ. f. med. Chem. u. Pharm.," 1893, Dez., pp. 488-492 u. 1894, Dez. p. 434-444.

335. VON HIRSCH. "Beitrag zur Organotherapie, Sperminum-Poehl, 1897," "St. Petersburg. med. Wochenschr.," No. 7. "Contribution à l'organothérapie et à l'étude de la Spermine-Poehl." "La Tribune Médicale." 1897.

336. URSZNYI. "O roosi Hetilap, 1898," 542, 556, 557, 585.

337. WICHTER, cf. Poehl. "Spermintheorie," p. 164.

338. Cf. § 88.

339. v. JAKSCH. "Zeitschr. f. klin. Med. Bd. xiii. 1888, p. 350.

340. DE RENZI. "Virch. Arch. cii.," 1882, p. 218.

341. PEIPER. "Virch. Arch. cxvi.," 1889, p. 338.

342. KRAUS. "Zeitschr. f. Helik." x., 1890, p. 100.

343. RUMPF. "Zentralbl. f. klin. Med." 1891, p. 441.

344. DROUIN. "Hémoalcalimétrie," Paris, 1891.

345. GRÄBER. "Klin. Diagnost. d. Blutkrankh.," 1888, Leipzig.

346. SCHERER. "Ver. d. Würzburg. med. Ges.," ii., Jahrg. 1852,

p. 325.

347. MOSLER u. KÖRNER. "Virch. Arch." xxv., 1862, p. 142.

348. BOCKENDAHL u. LANDWEHR. "Virch. Arch." lxxxiv., 1881, p. 561.

349. BOUCHARD. "Leçons sur les auto-intoxications dans les maladies." "Le Gendre," Paris, 1887.

350. LAUDER-BRUNTON. "Handb. d. allgem. Pharmakol. und Therapie," Deutsch von J. Zechmeister. Leipzig, 1893, pp. 74, 75.

351. ROBIN. ALB. "Journ. f. med. Chem. u. Pharm." 1898, Feb., p. 162.

352. NENCKI u. SIEBER. "Ueber eine neue Methode die physiologischen Oxydationen zu messen.," "Pflüg. Arch.," 1883, p. 319.

353. RICHTER. "Zeitschr. f. klin. Med.," Bd. 27, Heft. 3 und 4.

354. BUKOJEMSKI. "Journ. f. med. Chem. u. Pharm." 1892, Dez. pp. 63-72.

355. OSTROUMOFF. "Journ. f. med. Chem. u. Pharm." 1894, März, pp. 15-29.

356. PODKOPAJEFF. "Journ. f. med. Chem. u. Pharm." 1894, Sept., pp. 197-208 u. Dez., pp. 421-434.

357. KLIMONTOWITSCH. "Journ. f. med. Chem. u. Pharm." 1893, Juli, p. 343, u. 1894, September p. 153.

358. MORITZ. "Journ. f. med. Chem. u. Pharm." 1894, Sept. p. 153.
359. v. ROSSI. "Journ. f. med. Chem. u. Pharm." 1894, Sept. p. 153.
360. STANGE, *cf.* Poehl. "Spermintheorie," pp. 182-183.
361. v. NOORDEN. "Lehrbuch d. Pathol. d. Stoffwechsels," 1893, p. 212.
362. RUMPF. "Zentralbl. f. klin. Med." 1891.
363. DROBNY. "Russ. Arch. f. Pathol., klin. Med. u. Bakteriolog." Bd. II.
364. DÜRK. "Münchener med. Wochenschr." Juli, 1904.
365. HILTEBRANDT. "Case on the application of Spermin Essence" (Poehl) St. Petersburg Naval Hospital (Lecture delivered at the Society of Naval Doctors, St. Petersburg, Nov. 25, 1897 (Russian)).
366. ROSCHTSCHININ. "Sitzungsprotokoll d. St. Petersburg. med. Ges.," 26 Feb. 1891.
367. KLIMONTOWITSCH. "Journ. für med. Chem. u. Pharm." 1893, Juli, p. 343, u. 1894, Sept. p. 153.
368. GÜMLICH. "Zeitschr. f. phys. Chem.," 1891, p. 10.
369. ROBIN. "La fièvre typhoïde."
370. SHICHAREFF. "Protokolle d. St. Petersburg. med. Ges.," 26 Febr. 1891, "Journ. f. med. Chem. u. Pharm." (russ.) 1893, Juli, p. 347, u. 1894, Sept. p. 153.
371. BUKOJEMSKI. "Journ. f. med. Chem. u. Pharm." (russ.) 1892, No. 1, pp. 63-72, und *ibidem*. 1893, Juli, p. 348.
372. MAXIMOWITSCH. "Journ. f. med. Chem. u. Pharm." 1893, Dez., pp. 483-488, u. 1893, Juli, p. 158, u. 1892, Sept. p. 160.
373. BOGUSCHESKY. "Journ. f. med. Chem. u. Pharm." 1893, Dez., pp. 492-499.
374. HIRSCH. "Beitrag zur Organotherapie, Sperminum-Poehl." "St. Petersburg. med. Wochenschr.," No. 7, 1897. "Contribution à l'organothérapie et à l'étude de la Spermine-Poehl." "La Tribune médicale," 1897.
375. KOROLEFF. "Ref. aus. d. Wratsch" (russ.), 1897, No. 20.
376. MALINOWSKI. "Journ. f. med. Chem. u. Pharm.," Febr., 1898, pp. 213-215. Poehl, "Spermintheorie," p. 211.
377. OSTROUMOFF. "Journ. f. med. Chem. u. Pharm." 1894, März, pp. 15-29.
378. PROCHOROFF. "Journ. f. med. Chem. u. Pharm." 1893, Juli, p. 343.
379. SHICHAREFF u. HÜBENET, *cf.* POEHL. "Ein neues Stimulans, St. Petersburg. med. Wochenschr.," 1890.
380. DE BUCKE u. DE MOOR. "Thérapeut. Wochenschr.," 1897, No. 25.
381. SYMONS-ECCLES. "The British Medical Journal," 26 Aug. 1897.
382. BOSSE. "Journ. f. med. Chem. u. Organotherapie," 1904, January, pp. 143-146.
383. TSCHLENOW. "Wratsch," 1898, No. 9.
384. EGER. "Wiener klin. Wochenschr.," 1898, No. 6.
385. FRÉTIN. "Journ. f. med. Chem. u. Pharm." 1893, Dezember, pp. 465-468.

386. GOLDBERG. "Journ. f. med. Chem. u. Pharm." 1895, Sept., pp. 297-308, u. 1898, Feb. pp. 210-215.
387. PANTSCHENKO. "Journ. fur Med. Chem. u. Pharm.," 1893, Dez., pp. 468-492, u. 1894, Dez., pp. 434-444.
388. HIRSCH. "Beitrag zur Organotherapie—Sperminum-Poehl." "St. Petersb. Med. Wochenschr.," No. 7, 1897. Contribution à l'organotherapie et à l'étude de la Spermine-Poehl. "La Tribune médic.," 1897.
389. KLEMPERER. Verein f. inn. Med., 1 Juli, 1894. "Allgem. med. Cztg.," 1895, pp. 702 u. 714.
390. v. NOORDEN. "Lehrb. d. Pathol. d. Stoffwechsels," 1893, p. 212.
391. LEPINE. "Gaz. méd. de Paris," 1878, p. 149.
392. CANARD. "Essai sur l'alcalinité du sang dans l'état de santé et quelques maladies," 1879.
393. PEIPER. "Virch. Arch.," Bd. cxvi.
394. PREDTETSCHENSKY. "Ueber die Veränderungen des Blutes bei den Rheumatikern unter dem Einfluss von Schlammbehandlung in Saky. Diss. Moskau."
395. SHICHAREFF. "Journ. f. med. Chem. u. Pharm.," 1893, März, pp. 151-157, u. Juli, pp. 307-320.
396. v. ROSSI. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 347, u. 1894, Sept., p. 154.
397. GRETSCHANINOFF, cf. Poehl. "Spermintheorie," 1898, pp. 205-207. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., pp. 155-156.
398. FLEROFF, cf. Poehl. "Spermintheorie," p. 205. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 155.
399. v. JAKSCH. "Virch. Jahresb.," 1889, Bd. i., p. 247.
400. ROSCHTSCHININ. "Minutes of the St. Petersburg Medical Society in Russia," February 26, 1891.
401. STANGE, cf. Poehl. "Spermintheorie," 1898, pp. 206-208.
402. ROSCHTSCHININ. "Sitzungsprotokoll d. St. Petersburg. med. Ges." 26 Febr. 1891.
403. SHICHAREFF. "Sitzungsprotokoll d. St. Petersburg. med. Ges." 26 Febr. 1891. "Journ. f. med. Chem. u. Pharm.," 1893, März, pp. 151-157, u. Juli, pp. 307-320.
404. BUKOJEMSKI. "Journ. f. med. Chem. u. Pharm.," 1892, Dez., pp. 63-72.
405. FRETIN. "Journ. f. med. Chem. u. Pharm.," 1893, Dez., pp. 465-468.
406. OSTROUMOFF. "Journ. f. med. Chem. u. Pharm.," 1894, März, pp. 15-29.
407. SOKOLOFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., pp. 208-214.
408. PODKOPAJEFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., pp. 197-208, u. Dez., pp. 421-434.
409. KRIEGER. "Journ. f. med. Chem. u. Pharm.," 1895, März, pp. 76-91.
410. GOLDBERG. "Journ. f. med. Chem. u. Pharm.," 1895, Sept., pp. 297-308, u. 1898, Febr., pp. 210-215.
411. POSTOJEFF. "Journ. f. med. Chem. u. Pharm.," 1896, Jan., pp. 380-397.

412. DE BUCK und DE MOOR. "Das Spermin als Neurotonicum." "Therapeut. Wochensch.," No. 25, 1897, Wien.
413. SAWITSCH. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 334.
414. TULUSCHEFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 146.
415. MROTSCHKOWSKI. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 334.
416. MASLENNIKOFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 147.
417. SCHAFRANOFF. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 334.
418. BÖTHLINGK. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 147.
419. MORITZ. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 334.
420. SNAKOMZEFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 147.
421. MERTWAGO. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 334.
422. VIKTOROFF. "Journ. f. med. Chem. u. Pharm.," 1893, Sept., p. 147.
423. SPIEGEL. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 338.
424. PANTSCHENKO. "Journ. f. med. Chem. u. Pharm.," 1893, Juli, p. 338.
425. KONDRATJEFF, cf. Poehl. "Spermintheorie," St. Petersburg, 1898, p. 235. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 148.
426. FINKELSTEIN. "Journ. f. med. Chem. u. Pharm.," 1892, Dez., pp. 56-63, u. 1894, Sept., p. 146.
427. NAGUBNOFF, cf. Poehl. "Spermintheorie," 1898, p. 226. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 149.
428. AFROMOWITSCH. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 149.
429. MAXIMOWITSCH. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., pp. 149 u. 150.
430. TJASCHELOFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 151.
431. KOSTJURIN. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 151, u. 1896, Jan.
432. v. HIRSCH. "Beitrag zur Organotherapie, Sperminum-Poehl." "St. Petersburg. med. Wochenschr.," 1897, No. 7.
433. BENEDIKT, cf. v. Hirsch. "Beitrag zur Organotherapie, Sperminum-Poehl." "St. Peterburger med. Wochenschrift," 1897, No. 7.
434. EULENBERG, cf. v. Hirsch. *l. c.*
435. EWALD, cf. v. Hirsch. *l. c.*
436. FÜRBRINGER, cf. v. Hirsch. *l. c.*
437. MENDEL, cf. v. Hirsch. *l. c.*
438. KRAFFT-EBING. "Nervosität u. neurasthenische Zustände." Wien, 1895.
- 439 u. 440. SALOMON. "Ueber die Behandlung schwerer Neu-

- rasthenien mit Sperminum-Poehl." "Vortrag in d. Hufelandischen Gesellschaft." Berlin, d. 2 Febr. 1899. "Berl. klin. Wochenschr." 1899, pp. 744-747, u. 753, 754.
 441. BALLEET. "Journal des praticiens," 13 Aug. 1904.
 442. BUKOJEMSKY, s. No. 404.
 443. SHICHAREFF, s. No. 403.
 444. MAXIMOWITSCH, s. No. 429.
 445. TJASCHELOFF, s. No. 430.
 446. KOSTJURIN, s. No. 431.
 447. BENEDIKT, cf. v. Hirsch. "Beitrag zur Organotherapie, Sperminum-Poehl." "St. Petersb. med. Wochenschr.," No. 7, 1897.
 448. KONDRATJEFF, s. No. 425.
 449. DE BOOK u. DE MOOR, s. No. 412.
 450. HOFMEIER, cf. Poehl. "Spermintheorie," p. 227.
 451. BESPJATOFF. "Journ. f. med. Chem. u. Organother.," 1903, No. 27-28, pp. 85-87.
 452. LION. "Berl. klin. Wochenschr.," 1901, No. 52. "Journ. f. med. Chem. u. Organother.," 1902, März, pp. 9-27, u. 1903, März, pp. 29-45.
 453. FINKELSTEIN. "Spermin bei Morbus Basedowii." "Journ. f. med. Chem. u. Pharm.," 1895, März, pp. 92-98.
 454. POEHL. "Ueber den Einfluss des Spermins auf Autointoxikationen des Nervengewebes." Vortrag, den 27 Sept. 1894, "Ges. d. d. Naturf. u. Aerzte. Neurolog. Sekt. Wien. Verhandl.," p. 200.
 455. POEHL. "Die Nervenüberreizung als Ursache von Autointoxikationen." "Deutsch. med. Wochenschr.," 1901, No. 46.
 456. KRAFT-EBING. "Nervosität u. neurasthenische Zustände." Wien, 1895, p. 160.
 457. KOWALEWSKY, cf. Krafft-Ebing, l.c.
 458. KRAINSKY. "Zur Pathologie der Epilepsie." "Zeitschr. f. Psychiatrie, etc.," Bd. 54, 1895.
 459. RACHFORD. "New-York. Med. News," 1894, p. 12.
 460. LAUDENHEIMER. "Neurolog. Zentralbl.," 1897, No. 12.
 461. BECHTEREW. *Ibidem*, 1898, No. 7.
 462. LION. "Journ. f. med. Chem. u. Organother.," 1902, März, pp. 9-24, u. pp. 25-27.
 463. PANTSCHENKO. "Journ. f. med. Chem. u. Organother.," 1904, Jan., pp. 103-105.
 464. MAXIMOWITSCH. "Journ. f. med. Chem. u. Pharm.," 1894, September, pp. 149-150.
 465. WERBITZKY. "Russ. Medizin.," 1894, Nos. 29 u. 30. "Journ. f. med. Chem. u. Pharm.," 1894, Dec., pp. 404-412.
 466. v. HIRSCH. "Beitrag zur Organotherapie, Sperminum-Poehl, 1897. "St. Petersb. med. Wochenschr.," No. 7. Contribution à l'organothérapie et à l'étude de la Spermine-Poehl. "La Tribune médic.," 1897.
 467. EULENBURG. "Encyclop. Jahrbücher d. Gesamtheilkunde." p. 650, 1894.
 468. THELBERG. *Medical News*, 26 Mai 1900. "Wratsch.," 1900, No. 31, p. 943.
 469. JACOBY. "Journ. f. Med. Chem. u. Organother.," 1904, Jan., pp. 99-104.

470. POPOFF, L. F., *cf.* Werbitzky aus der Klinik von L. Popoff über die Wirkung des Sperminum-Poehl bei Tabes dorsalis. "Atasia locomotrix progressiva s. Tabes dorsalis." "Journ. f. med. Chem. u. Pharm." 1894, No. 4, pp. 404-411.
471. MAXIMOWITSCH. "Bemerkung über die therapeutische Anwendung des Sperminum-Poehl bei Arteriosclerose und Erkrankungen des Herzens."
472. ERB. "Verhandl. des Kongr. f. inn. Med. in Leipzig," 1904.
473. ROSCHTSCHININ. "St. Petersb. med. Wochenschr." 1890. "Sitzungsprotokoll d. St. Petersb. med. Ges." v. 26, Febr. 1891.
474. SHICHAREFF. "Sitzungsprotokoll d. St. Petersb. med. Ges.," v. 26, Febr. 1891.
475. KRIEGER. "Journ. f. med. Chem. u. Pharm." 1895. März, pp. 76-91 (Ref. a. d. med. Ges. in Chicago).
476. GOLDBERG. "Journ. f. med. Chem. u. Pharm.," Sept. 1895.
477. SOLOKOFF, "Journ. f. med. Chem. u. Pharm." 1894. Sept. pp. 208-214, Juni, 1897, pp. 60-64.
478. DE BUCK u. DE MOOR. "Therapeut. Wochenschr.," No. 25, 1897.
479. NAGUBNOFF, *cf.* Poehl. "Spermintheorie," p. 253.
480. WICHERT, *cf.* Poehl. "Spermintheorie," p. 253.
481. MAXIMOWITSCH. "Journ. f. med. Chem. u. Pharm." 1894. September, p. 150.
482. MRATSKOWSKI. "Journ. f. med. Chem. u. Pharm." 1894. Sept., p. 150.
483. VIKTOROFF. "Journ. f. med. Chem. u. Pharm." 1894, Sept., p. 151.
484. FRÉTIN. "Journ. f. med. Chem. u. Pharm." 1894, Dez., pp. 465-468.
485. ULRICH. "Journ. f. med. Chem. u. Pharm." 1894, Sept., p. 151.
486. KATZAUROFF. Briefl. Mitteilung, *cf.* Jakowleff, "Journ. f. med. Chem. u. Organother.," No. 22, 1900, pp. 39-103.
487. BELIOWSKY. "Berichte über Augenerkrankungen bei den Eisenbahnangestellten." "Zeitschr. f. Ophtalmologie," 1898, März und April.
488. BELJARMINOFF, *cf.* Jakowleff. "Journ. f. med. Chem. u. Organother.," No. 22, 1900, pp. 39-103.
489. JAKOWLEFF. "Zur Frage der therapeutischen Bedeutung des Sperminum-Poehl in der Augenheilkunde." "Journ. med. Chem. u. Organother.," 1890, No. 22, pp. 39-103.
490. DELOF, SERGIJEFF, *cf.* Jakowleff, *l.c.*
491. ROSCHTSCHININ, s. No. 473.
492. SCHULIN. "Journ. med. Chem. u. Organother.," 1904, März, pp. 89-94.
493. SHICHAREFF, s. No. 474.
494. KRIEGER, s. No. 475.
495. SOKOLOFF, s. No. 477.
496. SCHULIN, s. No. 492.
497. BELIOWSKI, s. No. 487.
498. SERGIJEFF, s. No. 490.
499. JAKOWLEFF. "Journ. f. med. Chem. u. Organother.," No. 22, 1900, pp. 39-103.

500. SNIEGIREFF. "Journ. f. med. Chem. u. Organotherapie," März, 1902, pp. 117-122.
501. LOMAKIN. "Journ. f. med. Chem. u. Organotherapie," 1904, Jan., pp. 99-100.
502. SCHULIN. "Journ. f. med. Chem. u. Organotherapie," 1902, März, pp. 89-94.
503. BOSSE. "Journ. f. med. Chem. u. Organotherapie," 1904, Jan., pp. 143-146.
504. ZAKRJEWSKY. "Journ. f. med. Chem. u. Pharm.," 1898, Febr. (Ref. aus "Journ. de Médecine de Paris," 1897, No. 8).
505. KLIMANTOWITSCH, s. Poehl. "Spermintheorie," 1897, p. 262.
506. NAGUBNOFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept., p. 149.
507. v. HIRSCH, s. No. 428.
508. PANTSCHENKO. "Journ. f. med. Chem. u. Pharm.," 1894, Dez., pp. 434-444.
509. KOSTJURIN. "Journ. f. med. Chem. u. Pharm.," 1894, Sept. p. 154.
510. FILIPPS. "Journ. f. med. Chem. u. Pharm.," 1894, Sept. p. 154.
511. PANTSCHENKO, *l.c.* No. 508.
512. KOSTJURIN, *l.c.* 509.
513. FILIPPS, *l.c.* 510.
514. MAXIMOWITSCH. "Journ. f. med. Chem. u. Organoth.," 1904, Jan., pp. 89-92.
515. ROSCHTSCHININ, *cf.* Poehl. "Spermin ein neues Stimulans." "St. Petersb. med. Wochenschr.," 1900.
516. PODKOPAJEFF. "Journ. f. med. Chem. u. Pharm.," 1895, März, pp. 85-113.
517. SOKOLOFF. "Journ. f. med. Chem. u. Pharm.," 1897, Juni, pp. 60-66.
518. GOLDBERG. "Journ. f. med. Chem. u. Pharm.," 1895, Sept., pp. 297-308.
519. HUCHARD. "Allg. Zentralzeit.," 1900, No. 75.
520. ZICKEL. "Lehrbuch der klin. Osmologie," 1894.
521. KULJABKO. "Versuche am isolierten Vogelherzen. Zentralblatt f. Physiol.," Bd. xv., p. 588, 1908, und "Berichte der Kaiserlichen Akademie der Wissenschaften," Bd. xv., 1901, St. Petersburg.
522. KULJABKO. "Studien über die Wiederbelebung des Herzens," "Arch. f. d. ges. Physiol.," Bd. 90, 461, 1892, und "Berichte der Kaiserlichen Akademie," Bd. xvi., 1902.
- KULJABKO. "Pharmakologische Untersuchungen am isolierten Herzen," "Vorläufige Mitteilungen der Akademie der Wissensch. St. Petersburg.," Bd. xvi., 1902.
- KULJABKO. "Weitere Studien über die Wiederbelebung des Herzens." "Wiederbelebung des menschlichen Herzens." "Arch. f. d. ges. Physiol.," Bd. 97, p. 539, 1903, und "Berichte der Kaiserlichen Akademie der Wissensch., St. Petersburg.," Bd. xvii., No. 5, 1892. "Zentralbl. f. Physiolog.," Bd. xvii., "Compt. rend. de l'Académie."
523. KAKOWSKY. "Ueber die Einwirkung verschiedener Sub-

stanzen auf das isolierte Herz 1904" (russ.). "Dissertation aus dem Laboratorium von Prof. R. Kobert in Rostock."

524. v. HIRSCH. "Beitrag zur Organotherapie, Sperminum-Poehl." "St. Petersb. med. Wochenschr.," No. 7. Contribution à l'organotherapie et à l'étude de la Spermine-Poehl. "La Tribune médicale," 1897.

525. SENATOR. "Die Autointoxikationen und ihre Behandlung." "Die deutsche Klinik." Prof. v. Keyden u. Prof. Klemperer. 2 Vorlesung, p. 3.

526. ROBIN, ALB. "Traité de thérapeutique appliquée." Paris, 1895.

527. BOUCHARD. "Leçons sur les autointoxikations." Paris, 1887.

528. PRAETORIUS. "Journ. f. med. Chem. u. Pharm.," 1895, Sept.

529. WELJAMINOW. "Sitzungsprotokoll d. St. Peterb. med. Ges." 26 Feb. 1891.

530. CHORWATH. "Mitteilung an d. Pariser Akademie der Medizin."

531. WELJAMINOW, *cf.* Chorwath, *l.c.*

532. POEHL. "Bulletin de l'académie Imperiale des Sciences de St. Petersbourg." Beilage. No. 2, zum T. lxxi., 1892.

533. KULJABKO, *l.c.* No. 13.

534. POEHL. "Journ. f. med. Chem. u. Pharm.," 1898, Feb., p. 330.

535. NAEBOB. "Arch. f. klin. Chirurg.," Bd. li. Heft 3, p. 646.

536. DESGRES, NICLOUX. "Compt. rend. d. l'Acad. des Sciences," 6 Dec. 1897.

537. POEHL. "Spermintheorie," 1898, p. 48.

538. PROCHOWNICK. "Münch. med. Wochenschr.," 1895, 30 Juli.

539. KRIEGER. "Journ. f. med. Chem. u. Pharm.," 1895, März, pp. 76-91.

540. PODKOPAJEFF. "Journ. f. med. Chem. u. Pharm.," 1892, Sept., pp. 197-208, u. Dec., pp. 421-434.

541. STANGE, *cf.* Poehl. "Spermintheorie," 1898, p. 277.

542. SOKOLOFF. "Journ. f. med. Chem. u. Pharm.," 1894, Sept.,

543. GOLDBERG. "Journ. f. med. Chem. u. Pharm.," 1895, Sept., pp. 297-308, u. 1898, Feb., pp. 210-215.

544. SCHICHAREFF. "Journ. f. med. Chem. u. Pharm.," 1893, März, pp. 151-157, u. Juli, pp. 307-320.

545. SIMANOWSKY u. SCHUMOFF. "Arch. f. d. ges. Physiol.," 33, pp. 251-264.

546. NENCKI u. SIEBER. "Jahresb. d. Tierchem.," Bd. 13, p. 330.

547. DONOGANY u. TIBALD. *J. ibidem.* 1894, Bd. 24, p. 552.

548. SHICHAREFF. "Sitzungsprotokoll d. St. Petersb. med. Ges.," 26 Febr. 1891.

549. SCHWIMMER. "Journ. f. med. Chem. u. Pharm.," Febr. 1898. Ref. in d. Ges. d. Hospitalärzte in Budapest.

550. WICHERT, *cf.* Poehl. "Spermintheorie," 1898, p. 281.

551. POEHL. "Die Eigenschaften des Harnes der Syphilitiker," 20 Sept., 1887. "Vers. d. Naturf. u. Aerzte." Wiesbaden, *cf.* Tagebl. d. 90. "Vers. deut. Naturf. u. Aerzte," 1887, No. 5.

552. v. ROSSI, *cf.* Poehl. "Spermintheorie," p. 284.

553. NIKOLSKI. "Russkaja Medizina," 1894, No. 30. "Journ. f. med. Chem. u. Pharm.," 1894.
554. BESSER, *cf.* Poehl. "Spermintheorie," p. 284.
555. MILAJEWSKY, *cf.* Poehl. "Spermintheorie," p. 284.
556. HOPPE-SEYLER. "Berlin klin. Wochenschr." 1892, p. 43.
557. QUINKE u. CANTANI. "Die Reaktion des Blutes bei Cholera-kranken." "Centrbl. f. med. Wissensch." 1884, p. 785.
558. SCHMIDT. "Charakteristik der epidemischen Cholera." Leipzig, 1850.
559. ROUX. "Thuillier et Nocard," "Compt. rend. de la Soc." biol. 1883, p. 565.
560. HÜPPE u. FAJANS. "Arch. f. Hygien." 1894, p. 20, 372.
561. KLEBS, EDWIN. "Die causale Behandlung der Tuberkulose," 1894. "Allgem. med. Zentralztg." 1894, pp. 760-762.
562. ARM. GAUTIER. "Les toxines microbiennes et animales." Paris, "Le Genre."
563. SENATOR, *cf.* v. Hirsch. "Beitrag. zur Organotherapie, Sperminum-Poehl," "St. Petersb. med. Wochenschr." 1897, No. 7. "Contribution à l'étude de l'organothérapie et à l'étude de la Spermine-Poehl," "La Tribune médic.," 1897.
564. BENEDIKT, *cf.* v. Hirsch, *l.c.*
565. HOFMEISTER, *cf.* v. Hirsch, *l.c.*
566. EULENBURG, *cf.* v. Hirsch, *l.c.*
567. EWALD, *cf.* v. Hirsch, *l.c.*
568. FÜRBRINGER, *cf.* v. Hirsch, *l.c.*
569. MENDEL, *cf.* v. Hirsch, *l.c.*

